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The Elderly Patient: Stress and Emergencies

Morris Kleinfeld and Joseph R. Wilder
Guest Editors

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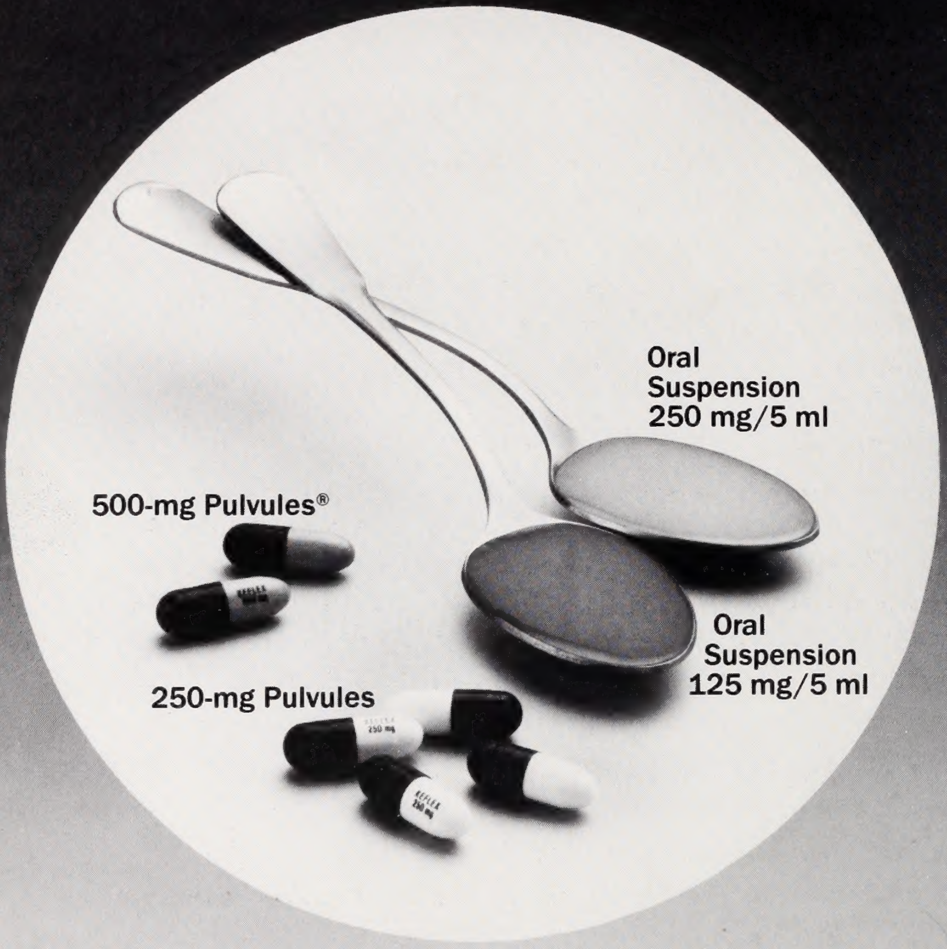
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The Elderly Patient: Stress and Emergencies

Surgical and Other Emergencies In Elderly Patients

THE MOUNT SINAI JOURNAL OF MEDICINE
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Surgical and Other Emergencies In Elderly Patients

Introduction

Great Britain as is frequently the case was one of the first countries to mandate a series of special health studies of the elderly as a group. In taking this action, Great Britain sent a clarion call to all governments that they had best become more involved in providing appropriate health care for the aging population. In the United States, Congressman Claude Pepper has provided dedicated leadership, inspiring both the government and the medical profession to pay more attention to this group. We are particularly pleased to have Congressman Pepper's very informative article to complement the collection of scientific papers in this issue, which concentrates on emergency care and stress in a host of problems affecting our older citizens.

In 1985, 36,355,000 major operations were performed in the United States. Approximately 33% or 10,612,000 were on patients over the age of 65. In order to better appreciate this staggering number, imagine the entire population of New York City, or twice the entire population of Israel, undergoing major surgery each year. There are approximately 25,000,000 people in the United States over the age of 65 and by the year 2000, we can expect 38,000,000. By the year 2050, one in three people will be over 55 years of age and one in four over 65 years of age in the United States. The problems confronting all of humankind in dealing with these staggering numbers are enormous; and the medical profession most certainly has its work cut out.

We have two major problems in relation to delivery of responsible health care to the elderly. First, how do we fund, educate, and recruit personnel sufficient to meet the needs of this population? Second, how do we inspire, attract, and provoke greater numbers of legislators, educators, and practising physicians to better focus on solving the enormous health problems presented by this unique group of human beings?

The article by Keller et al, "Emergency Surgery in Patients Aged over 70 Years," presented here, notes the finding that 20% or one out of five patients over 65 undergoing major emergency surgery died. Hirsch et al, in "Acute Appendicitis in Hospital Patients Aged over 60 Years, 1974–1984," found that twice as many patients in the over-60 age group arrived at the hospital with perforated appendices than did the under-60 age group. These are only two of many studies reflecting on some of the disturbing problems we are encountering in treating the elderly. We must focus on this group to find ways to alleviate their suffering. We must find answers. The articles in this issue are at once informative and provocative. They collectively send a clear signal to the health community: the health problems of the elderly are unique, challenging, frequently specific, and frequently require special knowledge for successful management.

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The papers in this section are all based on presentations at The Mount Sinai Medical Center, New York, on May 8, 1985, at the seventh annual Joel Hartley Memorial Symposium, supported by the Joel Hartley Memorial Fund.

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Health Care for the Elderly: The "Emergency Response" Approach

Claude Pepper

I have long believed that America possesses no greater responsibility than the assurance of quality health care to all citizens regardless of age or income. No group in our society is more dependent on our commitment to this responsibility than the elderly, as the following statistics will bear out:

- Over 80% of all older Americans have at least one chronic health condition. The most frequently reported chronic conditions include arthritis (44%), hypertension (39%), heart conditions (27%), visual impairments (12%), and diabetes (8%).
- The elderly use health care services at a significantly higher rate than the rest of the population. Persons over 65 use hospitals 2.8 times the rate of those under 65, and their hospital stays are nearly twice as long. People over the age of 65 visit their doctor an average of 4.3 times a year, whereas persons under 65 average 2.4 visits.

An important step toward fulfillment of that responsibility was the enactment of the Medicare and Medicaid legislation in 1965. With the creation of these programs, Congress established a sacred covenant with the American people—access to quality care shall not be limited by wealth or age.

Although there is little doubt that America's elderly have benefited from the vitally important Medicare program, there are problems. Expenditures by the elderly for health care have increased from 16% of their individual income in 1970 to nearly 20% in 1984. With this increase, average health care costs for elderly Americans have now returned to the same relative level as in 1965, when Medicare was enacted.

In addition, many essential health services are not covered by Medicare and are either only partially covered or not covered by Medicaid, as well. These services include the cost of drugs, eye examinations and eyeglasses, essential home health services and nursing care, foot care, routine physical examinations, and dental care.

And while the cost of services not covered by Medicare and Medicaid has increased and existing benefits are being reduced, we also know access to health care is being denied to many who need it. Government estimates show that 1 of every 10 Americans is without health insurance. The poor are two to three times more likely to be uninsured as the rest of the population.

Clearly we face a difficult challenge. We must maintain and improve the quality and range of health care services available to our nation's elderly while at the same time working to reduce spiraling health care costs. It is a challenge that can and must be met through our joint efforts. The elderly must be assured of our continuing commitment to providing them the quality health care they rightfully deserve.

We in the Congress are always looking for ways of cutting health care costs without jeopardizing quality of care. In scrutinizing our society's health care program for older Americans, many experts point out that it has from its inception been biased toward acute, institutional care.

The United States is spending well over $25 billion each year for nursing home care, roughly eight times the amount we spend for home care and support services. This institutional care is costly in both financial and human terms. An important goal of a good health program, one that seeks to provide a high quality of services at the most reasonable cost, is to maintain senior citizens in their communities and in their homes as

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long as is appropriately possible. Long-term care institutions should be the option of last resort.

A very high percentage of our oldest citizens are women who live alone. Approximately half of the noninstitutionalized women in the United States live alone. Approximately 25% of women over 65 are currently in nursing homes, and this number is likely to double by the year 2000.

Many of these older individuals have to be institutionalized when they develop functional limitations that may threaten their health and safety if they do not have immediate contact with neighbors and health and emergency services.

Personal Emergency Response Services. We can improve our health care system by reducing unnecessary institutionalization and improving the elderly's access to emergency assistance. An idea that has been proven to do this as well as to reduce ever-increasing health care costs is the personal emergency response system. To this end, I introduced legislation in 1985 that would be the first step toward making such a system available through the Medicare program.

The emergency response system allows the very frail and often the most vulnerable in our society to remain in their homes and communities by putting them in 24-hr contact with medical professionals and emergency services.

What are emergency response services?

An emergency response system has three basic components: first, electronic communication equipment in the home which automatically signals for help over existing telephone lines (the elderly person wears a monitor for this equipment); second, a 24-hour response center to receive the incoming alarms and send help when required; and third, local emergency response organizations such as visiting nurses, police emergency services, or individuals chosen by the user who agree to respond to specific calls for help.

The emergency response system, in the most basic terms, works as follows. A person in need of help at home presses the personal monitor he or she is wearing, activating the emergency base system at a hospital, health center, or comparable facility. The system base station then calls the person to determine the nature of the problem. If no response is received, a neighbor with a key to the dwelling is called, as well as the appropriate emergency response services. The emergency response will occur within minutes.

Each day the participating elderly person checks in with the base station. If the participant doesn't check in within a definite time, usually 12 or 24 hours, the system is automatically activated in order to make sure the person is still able to respond. Thus, he or she is always within contact of the base station in his or her home, even if unable to physically reach a telephone.

A study by the National Center for Health Services Research found that those elderly persons using personal emergency response systems: (1) required one day in a nursing home for every 13 needed by those not employing the system; (2) experienced a much lower rate of emergencies—roughly one-half that of those not using the system; and (3) felt much more comfortable living alone and more confident about continuing to live independently.

For the one-third of the population classified as severely functionally impaired and not socially isolated, each dollar spent for the use of an emergency response system produced a net savings of $7.19 in total long-term care costs, because of reduced use of institutionalization and community care.

Several studies have been reported. One study evaluated the emergency response system in California. It was primarily interested in behavioral responses. The leading reasons for using the emergency response system were falls and chest pains. Families felt less burdened, and recipients who were not socially isolated had improved feelings of security and control of their environment and reduced helplessness. No experimental trial of efficiency was done.

State and federal funding for emergency response systems has been obtained in nine states through section 2176 Medicaid waivers. The average cost is $25–$30 a month. In four states, local funding has been used. The Older Americans Act Title II program has also spent about $1 million on this service.

Most of the state and community reports are very favorable. Regrettably, there has been no good scientific evaluation of emergency response systems since the original NCHSR study. Other types of emergency response systems are being marketed. There is a perceived need for an emergency response system, especially for the frail elderly living alone. The systems will continue to expand and will have to be paid for—whether by Medicare, Medicaid, state agencies, Older Americans Act funds, voluntary organizations, or individuals and their families.

There is a critical need for scientific evaluation of these systems. There is a very real probability that the system will be of substantial health and social benefit to frail elderly and possibly reduce institutionalization. A very limited evaluation is being proposed as part of the social health maintenance organization (SHMO) demonstration, but this will not evaluate such a system's efficiency in the community. The bill establishing this service I introduced in 1985, H.R. 1223, died in committee. I will introduce a similar bill in the 1987 session of Congress, which will provide for a good scientific evaluation of both the costs and health benefits of emergency response systems. The results of the study will provide a sound basis for the selection of individuals who will benefit from the use of such systems, the cost per patient, and the rationale for future implementation of the program. It currently enjoys the support of members of Congress.

It has been estimated that 40% of all nursing home admissions could be avoided if proper services were available in the home and community. For the psychological and financial gains this could bring if it were accomplished, I believe we need to put a high priority on the testing of emergency response systems.

We must look beyond the acute, institutional bias of our current programs to the availability of preventive services and community- and home-based care. We must not only maintain our commitment to the poor and elderly by defending Medicare and Medicaid—we must find ways to make these essential programs better.

America is one of the richest nations on earth. It is only fitting that we devise a way to completely and equitably provide health care for our citizens.

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The Longevity Revolution

ROBERT BUTLER, M.D.

From my point of view Congressman Claude Pepper is one of the pioneers of what I have these days been calling "the longevity revolution." I know we often use the word "model," maybe too commonly; nevertheless I must use it—Congressman Pepper is an extraordinary model of what one can be as a productive citizen throughout life. In 1985 we inaugurated in the Department of Geriatrics at Mount Sinai a Center for Productive Aging to help us begin to look at the important connection between being productive and healthy and being nonproductive and unhealthy; clearly, these are interrelated states. The concept of taking care of one's self and building one's own way throughout life, including late life, that Claude Pepper refers to, is vital. Without a sense of purpose, and without a sense of contribution, and without society benefitting from that contribution, we really miss out on life enormously.

The Demographic Revolution. "Revolution" is another word that's often overused. Yet if we mean by it a fundamental change, we are indeed experiencing a revolution, extraordinary fundamental change, in demography in this century.

Life Expectancy. As Claude Pepper points out, when he was a boy, the percentage of older people was relatively lower than it is today. We have gained a dramatic twenty-five years in life expectancy since then. We are going to have to make remarkable and necessary adaptations to such a change. What was once the privilege of the few has become the destiny of the many. Women in particular are increasingly living longer; now at birth their life expectancy exceeds that of male babies by 7.3 years, and it would appear as we move into the next century that the differential will reach ten years. But young women aged between 18 and 24 years are showing some unfortunate consequences of the higher incidence of smoking among women; reports from various states, Texas for example, show that for the first time cancer of the lung is surpassing cancer of the breast as a cause of death among young women. If we can just gain some control over that, we will continue to see this extraordinary difference in life expectancy.

The Baby Boom Crest. The baby boom group is something to behold. Those born between 1946 and 1964 were 76 million strong; 70 million of them still survived in 1985. In roughly the year 2020, when they crest, 55–60 million of them will be over 65. In short, when the baby boomers reach Golden Pond, we are going to have a very different society, culturally, economically, medically. The concept that older people will be 20% of the population could well be an underestimate. Demographers throughout the twentieth century have tended to underestimate the presence of older persons, and that could well happen again with any breakthroughs in treating the major physical threats to the elderly—cardiovascular disease, cancer, and so on.

Reduction in Deaths. The reason for this longevity revolution has been the unprecedented drop in maternal deaths, infant mortality rates, and childhood mortality rates. Perhaps less recognized is the fact that between 1968 and 1981 there was a reduction of 13% in deaths from all causes, a reduction of 48% in deaths from stroke, and a reduction of 30% in deaths from heart attack. Some 800,000 people who might have died of heart attacks since 1968 have not done so. That is another phase of this longevity revolution that moves beyond the changes in mortality rates related to earlier years of life—a function, we think, of health promotion and disease prevention, but also clearly of the advent of Medicare

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and Medicaid. Those social legislative achievements opened the door to medical care for people, older people, who simply did not have available to them that care in the past. Eighty percent of all deaths now occur in people who are over sixty years of age. In 1830, when the United States was a Third World nation, one of three newborn babies lived out what today we take for granted, a full life of 60 years. Today eight of ten newborn babies live out that life.

Lifespan vs. Life Expectancy. It is important to distinguish clearly between lifespan and life expectancy. Lifespan is the inherent natural length of life in a species; in humankind it's probably 100 to 110. We need to have Claude Pepper around a long, long time. The difference between average life expectancy today in the United States and the natural lifespan is about 35 years. So if we could gain 25 years for average life expectancy in this century, I don't think we should be a bit surprised that, with the growing understandings of the new biology, molecular biology, and immunology, we're going to begin to harness a better understanding of the biological mechanisms of senescence, which predisposes to disease and disability, to increase survivorship.

Disability-Free Life Expectancy. And that's what's happening—increasing survivorship, not an increase in the natural lifespan. Everyone points out that there's no great advantage to living long if you don't live well; it's the quality of life that becomes important. A new concept, disability-free life expectancy, or active life expectancy, is important to hold in mind. In America, where the average life expectancy is 74, the average disability-free life expectancy is 72. This simply means that on the average, we experience about two years of morbidity prior to death. We want to make the morbidity less profound. We want to shorten the period of morbidity. And that certainly is one of the goals of the marvelous collective biomedical enterprise called research, which Mary Lasker, among others, and Claude Pepper, who does not give himself full credit, have done so much to inspire and build in this country.

The longevity revolution is not unique to the United States nor to the industrialized nations. It's a worldwide phenomenon. Sixty percent of all people over sixty will be Third World people by the year 2000—which is just around the corner. I have had the good fortune to have traveled to many lands and to have seen the state of awareness of the aging of the population. I can tell you that no society—not one—is fully prepared; the threshold of consciousness and awareness is just beginning to be reached. This demographic change is a watershed; little wonder that adaptation will take some time. Remember that the response to the industrial revolution—Cartwright and the spinning jenny, Watt and the steam engine—which was begun 250 years ago, hasn't yet been completed. We still have industrial slums, and we still have pollution, and we still live with the consequences of the separation of the family from the workplace. So a transition to the longevity revolution is going to take some time.

Health Care. Now some brief remarks about a few necessary responses of the health care industry itself as broadly defined, about the kinds of changes that are going to have to come about if we are going to responsibly meet the challenge posed by the absolute number and relative proportions of older persons.

One, insofar as geriatrics is concerned, is the education of health providers. Geriatrics is not the same as geriatric medicine, or geriatric psychiatry, or geriatric surgery. It is not better than any of them, but it is different. It cuts across many disciplines. It speaks to the variety of resources, specialties, providers who must work together in a team approach to do what's required to meet the profound, multiple, complex, interacting physical and psychosocial pathologies of old age. Aging itself has profound effects, even though we try hard to deny the realities of those effects on our physiology and behavior. Aging comprises such profound processes that they do predispose not only ultimately to death, but to a range of disease and disability. There is the high incidence of Alzheimer's disease, and of long chronic illness; the fact that 81% of all cancer occurs in people over 51 years of age, and that 50% occurs in people older than sixty-five; the fact that benign hypertrophy of the prostate is almost ubiquitous in men who live on to their seventies and eighties. One could go on pointing out the extent to which an array of diseases that have not yet received the steady scrutiny of science are influenced by the role of aging in pathogenesis. We must understand those fundamental biological processes better.

Broadly defined, then, geriatrics involves the psychological, social, behavioral, and nursing aspects of health care, and it must integrate services. It involves the application of gerontology, the studies of aging, from the biological, psychological, and social perspectives; and it focuses specifically on the concept of the continuum or the spectrum of care. In our own program here at

Mount Sinai, we've been trying to build toward assessment, health promotion and disease prevention, acute care, subacute care, emergency care, long-term care, and rehabilitation. And to try to have all those foundation stones in place and, as an academic department, to look at ways of enhancing the quality, the speed, and the character of care.

Obviously we're going to be moving toward geriatrics subspecialization within the various fields of medicine. The view of Dr. William Kelly, chairman of the American Board of Internal Medicine, on the issue of geriatrics subspecialization within internal medicine, which I share, is that internal medicine, and perhaps surgery, family practice, and psychiatry, do need a group of passionate subspecialists in geriatrics who are going to constitute the leaders. We need those leaders. We need them to build programs, to innovate new forms of service delivery, to be the teachers and to be the contributors of new knowledge. In my judgment we do not need a brand-new practice specialty called geriatrics. I see no advantage to our absolving present primary care and specialty groups from carrying on the medical care of older persons. And I see no reason why any of us should at some arbitrary age—65, 70, 80—be turned over to a brand-new doctor. But we physicians must be sure that we have the academic leadership that systematically inculcates in all of the physicians who are in training—undergraduates, postgraduates, and practitioners, in continuing medical education—the kind of knowledge they're going to need to respectfully and effectively meet the medical and social needs of older people.

For twenty years, Medicare has provided funds for graduate medical education. That funding is coming under serious question today. And Senator David Durenberger of Minnesota has been actively looking at current spending—nearly $2 billion—for graduate medical education. Not one nickel of Medicare funds has ever been spent specifically to support geriatric medical education; those funds have been used to support graduate medical education as a whole. To quote Senator Durenberger, "Medicare expenditures should benefit Medicare patients." In an analysis I did, I found that some obstetrics deliveries were paid for under Medicare. It means some extraordinary things have happened in the use of Medicare funds.

In 1980, the Rand Corporation in a major manpower study projected the need for leadership in geriatrics at approximately 10,000 by the year 1990. That's not many. In 1990, there will be about 575,000 physicians; 10,000 of that number is indeed a very small fraction. There are some 7,000 skilled nursing facilities in the United States, for example, that should have medical directors. There are 127 medical schools that should have centers of outstanding teaching to insure excellence.

Proposal: National Fellows in Geriatrics. My proposal is that we now utilize the Medicare funds in graduate medical education to establish a national fellowship program in geriatrics, in the various subspecialties that I've already outlined. And we could move very quickly to meet the Rand Corporation's desires and goals by supporting 2,000 geriatric fellows per year in two-year cycles. Over a ten-year period, five cycles, there would be 10,000 geriatricians. Now that's some five years later than the Rand Corporation proposed, but the idea has come about some five years later than the Rand Corporation's suggestion. One hundred twenty-seven medical schools could train 15 fellows each. That's all they would need to do in order to fulfill this goal.

Such a program could be set up differently from other fellowship programs, through some competition in which those schools that built outstanding programs would be the ones that would have the fellowships. The costs would actually be modest: $54 million for the entire training of 10,000 geriatricians, plus some developmental money to establish the training programs themselves, for a total of about $80 million. That's a modest fraction of the total $2 billion now spent for graduate medical training. In fact, the Medicare total will be $3 billion in 1986, 1987, and 1988.

Organizational Changes. The longevity revolution is going to require of us some major organizational changes. First, we need systems changes, changes in the way in which we deliver care to older people. Changes are also involved in the use of new technologies, which are supremely important in surgery and emergency medicine—technologies that capitalize on microprocessors, techniques of dealing with the deficits (sensory, mobility, communicative) that significant numbers—but not all—older persons experience. Third, major shifts in reimbursement mechanisms will be required. There may be no new dollars brought into the health care system in the near future. So we're going to have to make shifts more in keeping with the character of the population that is growing and needs to be served: more attention to home care and to long-term care;

more attention to broad processes of assessment, maintenance, and restoration of functon.

Some of these changes are going to be quite surprising, and they're going to come very quickly. You're going to see the emergence of more and more HMOs (health maintenance organizations) and SHMOs (social health maintenance organizations), and a greater development of social services, especially in coordination with medical services. And the development of lifecare communities, not only in rural and suburban areas but in urban settings.

We do have to be careful during this transitional period that we don't put cost containment in overdrive. We've had a lot of anxiety within our own department over potential and actual denials under the PRO system, for example, of persons who clearly require important care. We admitted an 84-year-old woman who was confused, nearly blind, and who was setting fires—not on purpose—in her home. She was clearly a danger to herself and a danger to others who lived in the building. Will the hospital be reimbursed for her admission? Will she be regarded as a social admission? A psychiatric admission? A medical admission? In the absence of appropriate holding stations, say, attached to emergency rooms, in the absence of adequate shelter, in the absence of other options available, how do we meet the needs of such a person?

Research and Cost Effectiveness. Next, we have to significantly reorder the research agenda in this country. The National Institute on Aging, the newest of the National Institutes of Health, now accounts for 2% and only 2%, of the entire budget of the National Institutes of Health, despite the high correlation between disease, disability and age, and the extraordinary costs of one disease alone—Alzheimer's disease, which probably accounts for half of the people in nursing homes. In fact, the fastest growing of all health costs in the country is the cost of nursing home care; these homes now contain more patients on any given day than do hospitals.

Along with genetics, and environment, aging is the third of the three major antecedents to the pathogenesis of disease. It's clear that we're not capitalizing on the cost-effective approach of supporting research on aging. If we gain control, for example, of the immune senescence which grips us all with the passage of time, we could be affecting a whole range of diseases, not just one, as in the classic biomedical disease-of-the-month approach.

Promotion of Health. Finally, we have to spark even further the promotion of health as a means of preventing disease. Promoting health is not just for young people. Throughout life, people can and do increase their own capabilities. Dr. Libow and I, in studies we did in the 1950s at NIH, found that when even long-standing smokers who had smoked three and four packs of cigarettes a day stopped smoking, their pulmonary function could return nearly totally within a year.

Emergency Room. The emergency room is frequently the source of medical care that many older people have to use. We need to create outposts in housing sites, geriatric assessment units, community outreach units that will begin to prevent the unnecessary and expensive flow of older people into emergency rooms. We need to identify ahead of time the high-risk older person: 85 years or older, with a variety of other particular physical characteristics, including socioeconomic ones. We need studies of an epidemiologic character, of an economic character, to better understand the risk profile. We need to think of techniques such as Sir Ferguson Anderson introduced in the United Kingdom many years ago: having community health workers assure that patients at possible risk are picked up long before they have to resort to the emergency room.

Once the person is at the emergency room, we have to develop techniques for holding that person overnight, or several days if necessary, perhaps as an outpatient reimbursement rather than the expensive in-house admission, which is often not so good for older people anyway. They do best by being on their feet and outside an institution as long as possible.

Comprehensive Health Care for All. This century has been an extraordinary one. We should be celebrating two great legislative achievements: the 51st anniversary of Social Security, and the 21st anniversary of Medicare. Yet at a time of increasing numbers and an increased proportion of older persons in our population, we must worry about the preservation and the strength of these agencies. We must move toward a set of major reforms that will bring us finally to a comprehensive health care system that doesn't leave the elderly out in the cold, doesn't gentrify the health care system, doesn't cream-skim, and doesn't leave out of the health care system those who are poor and disadvantaged, especially older women, simply because they happen to be the survivors who have grown old.

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Ethical Issues in the Emergency Care of Elderly Persons: A Framework for Decision Making

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The following cases describe part of the broad range of ethical issues concerning elderly persons in emergency room situations. Not all are the dramatic life-and-death decisions that make headlines, but all are difficult—sometimes agonizing, sometimes simply annoying, but always frustrating. To put these problems in a framework of ethical principles will help us reach a more satisfactory and ethical solution, will provide better patient care, and will also decrease frustration.

Case 1. A 77-year-old man with a history of arteriosclerotic cardiovascular disease and probable multiinfarct dementia, capable of no self-care and who does not recognize his family, is brought from a nursing home obtunded, febrile, and dehydrated. His respirations are labored and slow. No family members can be found, and apparently they have not visited for several months. How aggressive should we be in his care?

Case 2. An 82-year-old eccentric woman with gangrene of one leg refuses the amputation recommended by the surgeon. She says she does not want to be hospitalized and yet has no apparent place to go and is making no moves toward the door. Is she competent to refuse therapy?

Case 3. An 86-year-old man who has been living independently and doing well in the community is brought in after collapsing on the street and being resuscitated by a bystander. Someone who knows him reveals that he has a history of cancer and that he has signed a "living will." What does that mean about what we should do?

Case 4. A 78-year-old woman brings in her 84-year-old husband. He is too weak to get around. His alertness has been declining, and he has urinary incontinence. You ask, "How long has he had these problems?" and she says, "About a year, but I just can't take care of him anymore." What's the responsibility of the emergency room in this kind of case?

These are just a few of the many sorts of problems that we see with elderly people in the emergency room. There is a systematic way of thinking about each one of these problems. Three principles—beneficence, respect for persons, and justice—are the key principles we need to keep in mind to analyze these ethical dilemmas (1); most dilemmas are, in essence, a conflict between two of these principles, where one must choose which should prevail and be able to give a rational justification for that choice:

- **Beneficence:** the current tradition of medicine; "do no harm"; the patient's best interest comes first; the physician's primary responsibility is to the patient.
- **Respect for persons:** the social libertarian tradition; patients' rights; informed consent; the right to refuse treatment; the right to die.
- **Justice:** the "triage" tradition; fair allocation of resources; physician as gatekeeper; rationing: implicit and explicit.

Beneficence, the most ancient of these principles, is far older even than the Hippocratic tradition, and simply means, Do good and do no harm. It is the primary ethical motivation for most of us in the helping professions.

The second principle, respect for persons, has

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a much more recent history. It represents the concern for liberty and self-determination on which our country and our Constitution are based. It is also the basis of our legal system, which exists to maintain the rights of individuals to self-determination as long as that self-determination does not impinge on the rights of others. You may already see how conflicts can arise between beneficence, the ancient duty to do what is best for your patient, and respect for persons, the more recent and strongly legally supported principle of respecting the patient's right to make his or her own decisions.

Justice is the concern for fair allocation of scarce resources. How does that fit in with a tradition and a profession that has sworn always to put the patient's interests first? The exception to this, which is very important in emergency care, is particularly seen in wartime, the context in which the word "triage" originated (2). In the emergency room of a large city hospital are we doing triage? On the battlefield, the major goal is to treat those capable of returning to the fighting, where those who might survive with a great deal of attention and resources will probably be neglected. What is the relevance of this principle to modern medical care?

CPR: Beneficence vs Respect for Persons

Beneficence is consistently the major focus of the tradition of Maimonides and Hippocrates. It says to do no harm. It says the patient's best interests come first. It says the physician's primary responsibility is to each individual patient. A fragment from the Hippocratic tradition counsels, "you will exercise your art solely for the cure of your patients" (3); that counsel is now, according to many ethicists, obsolete (4). Because of technologic advances and the increasing prevalence of chronic diseases, cure is not the relevant goal in many modern medical situations. Because of our presumption of the right of competent persons to make their own decisions, our responsibility to try to cure disease is tempered by the need to consider the patient's own sense of the risk-benefit analysis of any proposed treatment.

The practice of cardiopulmonary resuscitation brings into sharp focus the extremes of risk and benefit and the role of uncertain outcomes in our decision making. In a concern about who should receive cardiopulmonary resuscitation (CPR), the American Medical Association has stated, "The purpose of CPR is the prevention of sudden, unexpected death. CPR is not indicated in certain situations such as in cases of terminal, irreversible illness where death is not unexpected. Credible medical support for this view has been offered. It has even been suggested that resuscitation in some circumstances may represent a positive violation of a person's right to die with dignity" (5). This statement really calls into question the simple notion of beneficence and means that we have to begin to think about beneficence in a much more complex fashion.

In a situation in which death is inevitable, should we ever not intervene? Yes—if the prospects of survival are so poor that CPR would extend life only briefly and painfully (beneficence), or if the patient refuses (respect for persons). The question is so complex that the State of New York has formed a commission to deal with issues of how hospitals ought to handle decisions about the end of life, and in particular about resuscitation and life-sustaining procedures. Hospitals all over the country are trying to develop policies for dealing correctly with these decisions. Such policies, of course, need to be different in some important ways for care in the emergency room. An open and well-thought-out set of guidelines or policies can be very helpful to emergency physicians faced with awesome decisions on behalf of patients they do not know.

Are regulations and policies, however, the right way to handle these difficult, personal, and intimate questions? Ideally, we would not need external legalisms. For example, if advance knowledge exists about the patient's own wishes, we can then look to respect for persons as being our primary guide in decision making. How can we ensure that we have that information? Not everyone agrees about the public-policy implications supporting advance directives, such as living wills (6) and designated proxies in the form of durable powers of attorney (7), but these mechanisms could distinctly enhance patient autonomy in the event of incompetence. Many physicians and other health professionals feel that our responsibility is to prolong life at all costs. The debate goes on, and it focuses on this single question—who decides? Answers will be difficult to arrive at through broad policy statements alone. Ideally, such answers are arrived at in the context of each clinical situation. But this requires that clinicians will have to understand how to use philosophical language, how to reason analytically about value choices, how to better understand the law, how to discuss these difficult questions with candor and sensitivity, and how to relate to our patients better in order to enable joint decisions whenever possible.

Forgoing Treatment

One strategy for analyzing decisions to limit treatment, especially decisions to forgo life-sustaining treatment, developed by a philosopher and a physician (8, 9), is a useful format for analyzing the components of such decisions. That strategy suggests the following four potential reasons why one might decide to forgo life-sustaining treatment for a particular patient, arranged in a hierarchy based on the principles of beneficence, respect for persons, and justice:

1. Medical futility.
2. Patient refuses.
3. Quality of life.
4. Cost of care.

The most acceptable ethical argument for not doing something is medical futility. We do not have any obligation to give people something that will not work, and in fact, we may have an obligation not to ("do no harm"). The problem, of course, is that in many clinical situations data are incomplete, and we are often making decisions in a situation of enormous uncertainty about risks of treatment, as well as risks of nontreatment. In great uncertainty, we have to decide who is taking the risk and, whenever possible, allow the patient to consider the risks himself. The moral preeminence of medical futility as a basis for decisions is really a claim for better data (that is, for better research) (10) about the outcomes of interventions, particularly emergency life-sustaining interventions in elderly persons. If we could know for sure that something would not work, we would have a much easier time deciding not to do it.

The second possible reason to forgo life-sustaining treatment is if the patient declines to accept treatment. This refers to the principle of respect for persons and the legal tradition of support for self-determination. "Every adult of sound mind has the right to determine what should be done with his or her own body" said Justice Benjamin Cardozo in 1914, in a malpractice decision against a surgeon who operated without obtaining valid informed consent (11). If the person is not of sound mind, we have a different sort of responsibility, based largely on trying to establish what that person "would have wanted" (respect for persons) (12).

The third and fourth reasons are of much more highly questionable ethical validity. Are we really in a position to make quality-of-life decisions for someone else? When the patient refuses treatment because of his or her own concerns about quality of life, that refusal has to be acceptable if we believe that we should respect the patient's wishes. But can we, on our own, decide that the quality of life of someone else is not worth living (13)? Such an assessment is inherently subjective and confronts our values of respect for individuals and respect for life itself.

The fourth reason, the cost of care, is even more ethically difficult. Health care professionals have never before been in a situation of making treatment decisions based on balancing the federal budget, and now we are. We are finding that a very uncomfortable position, because it conflicts with our basic roots in ethics and law (14). The battlefield is quite a different situation; there are finite resources and scarcity is dire, yet your job is to get people back into the fight again. That is not what is happening now in our cities' emergency rooms; there, scarcity is relative, not dire, and we physicians have an obligation, both legal and ethical, to do what is best for our patients. The President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research has asserted that society may decide to limit the availability of certain options for care in order to advance equity or the general welfare. That is to say, we may decide we have to cut back on some aspects of medical care if it costs too much and we decide other aspects are more important or more cost-effective. But such policies should not be applied initially or forcefully to medical options that could sustain life. The emergency room is not the place, the life-or-death situation is not the time, for us to be thinking about balancing the federal budget. In fact, because what is at stake is so enormous and because there is no time for thoughtful reflection, we should look elsewhere first when we talk about cutting costs (15).

Data on CPR in Practice

Cardiopulmonary resuscitation is an intervention which holds many of these ethical issues, and which is coming under great debate and scrutiny (16). In 1980, a questionnaire was administered to emergency room physicians about how long they would pursue a resuscitation attempt in various categories of patients (17). In patients over 65, only 4% would cease CPR early. In a patient over 75, 9% would. In a patient from a nursing home, 18% would. In a patient who is senile, demented, or mentally retarded, 54% would. With end-stage chronic obstructive pulmonary disease or malignancy, 87% would cease CPR early.

These choices seem to indicate somewhat different criteria from those I have been discussing. Physicians are making quality-of-life decisions if they decide that someone from a nursing home should not get as aggressive a resuscitation attempt as someone who is living in the community, or if they base a decision on chronological age. Value judgments are expressed here which need to be examined.

The overall increased life expectancy of the past two decades has been accompanied by extensions of the capacity to live an active and an independent life. Sidney Katz and colleagues studied active life expectancy in the elderly (18). People aged 70–74 have an average active life expectancy of 8.1 years. Even at the age of 80–84, the average active life expectancy is 4.7 years, almost five years. How many decisions do we make for cancer patients, for example, in which 5 years seems like an enormous amount of time? For that group, 5 years seems like enough time to justify extraordinary measures. In fact, in cancer statistics, 5 years of survival is often a measure of successful treatment, even though it does not imply "active" or "independent" survival. We need to develop a more complex understanding of what life expectancy means in old age, because the demographic shifts occurring now are going to change our society and our concepts of medical care in unprecedented ways.

Another study, done at a Veterans Administration Hospital, looked at patients who actually had do-not-resuscitate orders on the chart and found that the conditions that correlated with such an order were neoplasm, nonambulation, urinary incontinence, and dementia (19). Interestingly, age in itself was not statistically significant. But very important quality-of-life judgments seem to have been made. Another questionnaire on a hypothetical situation asked physicians which sorts of patients they would be more likely to resuscitate (20). The investigators developed and included in the questionnaire a scale of prognostic equivalency of diseases so that heart disease or cancer patients, say, could be compared for life expectancy. By the responses, the house staff would resuscitate fewer cancer patients, even after the prognostic equivalency was known. The diagnosis of cancer makes a general group of physicians less willing to be aggressive. Oncologists, however, resuscitated cancer and cardiovascular patients similarly, and cardiologists and pulmonologists resuscitated cardiovascular patients more than cancer patients of the same prognostic equivalency. Thus, the attitudes that we physicians hold about various diseases play a role in our decision making. It would be interesting to compare a group of emergency physicians with other groups of physicians.

All the data on outcomes of CPR reveal enormous uncertainty in predicting outcomes and high morbidity associated with "successful" resuscitations, especially in patients of advanced age. Because of clinical uncertainty, it really has come to be accepted that the voluntary choice of a competent and informed patient should determine whether life-sustaining therapy will be undertaken (14). Patients are not entitled, however, to insist that health care practitioners furnish them with services when to do so would breach the bounds of acceptable practice or violate a professional's own moral beliefs, which is to say that informed consent has to work within the context of good medical decision making. Valid informed consent consists of full information, patient choice which is free and not coerced, and a competent patient. These criteria are often difficult to meet in emergency situations. For incompetent patients, the best basis for decision making is to have some sense of what that patient would have wanted in this situation, consistent with the principle of respect for persons. The ideal situation, of course, is that we know the patient over time and, as the caregivers, have a sense of how to respect that patient's wishes. But without a long-term relationship, the next best thing is probably some sort of advance directive, a living will or durable power of attorney. Even though the living will has not yet been tested in court, it has been legalized in 23 states and gives a care provider important information about making these decisions (6). The durable power of attorney is available in all states, but not in the District of Columbia, and allows a person to designate a proxy decision maker. This device has not been directly aimed at health care decisions, except in recent legislation in California and Pennsylvania (7).

A proxy or surrogate decision maker not specifically designated by the patient is much more problematic. Turning to the family for life-and-death decisions in a time of great stress is not good, either for them or for the quality of the decision.

We can improve our systems of health care and, in particular, our systems of delivering emergency care so that more ethical decision making is possible. Many ethical decisions will never be easy, nor should they be. They should always remain difficult, because we are human and caring. But we should be able to justify the decisions we make, and to feel secure in that justification. Our training of people who will be caring for the elderly in the years to come must change if we are to improve our decision making about ethical matters. The president's commission feels that improvements in the relationship between health care professionals and patients must come not primarily from the law, but from changes in the training of health care professionals themselves. We do not, in this view, necessarily need to teach more law, but we do need to foster better relationships and develop structures of health care that can give the kind of continuity necessary for respect of patients' wishes. We need to teach enough ethics so that the basic principles become part of clinical decision making. In changing the way we relate to elderly people, not only in the emergency room but in the hospital, in the nursing home, and in the community, we have to be teaching a more complex notion of the idea of physician, one able to go beyond technical skills into the qualitative world of human culture and individual values. In an advanced civilization which creates increased life expectancy as well as greater technical capability to sustain life, even against all odds, that complex notion does not necessarily imply heroism, extraordinary care, or extreme measures. It does, however, as Cassem asserts, imply that "even when we decide that our advanced technologies are no longer indicated, we can still agree that certain extreme measures are indicated. Extreme responsibility, extraordinary sensitivity, and heroic compassion" (21).

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Suicide Risk in Elderly Persons: Diagnosis and Management

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Abstract

Clinical experience suggests that suicidal thought in the elderly is transient and restitution of premorbid function is possible. Consequently, efforts to prevent suicide are obviously worthwhile. Knowledge of the pertinent psychological theory and the composite clinical profile and careful interviewing techniques make suicide intervention in this age group a realistic goal.

It is clear that older Americans are deadly serious about killing themselves (1).

Suicide is the 11th most common cause of death in the United States. People over fifty make up a little more than one-fourth of the total U.S. population, yet account for almost 40% of deaths by suicide. Moreover, there is the suspicion that many additional suicides are unreported or misdiagnosed.

Unlike their younger counterparts, the elderly have a real sense of ending their lives. In adolescent suicide, the rate of attempt-to-success is about 100:1. Over age 60, the attempt-to-success ratio approaches 1:1.

Pragmatically, I believe that suicidal thought is for the most part transient. Whether from hopelessness and despair, illogical reunion fantasy, or cognitive impairment, the altered psychological state should be considered temporary. Accordingly, vigorous attempts should be made on the person's behalf to reverse the prevailing state of mind.

This paper reviews the psychological theory about suicide, the characteristics most common to the elderly who take their lives, interviewing techniques that help determine who is most at risk, and initial medical management.

Dynamics and Clinical Profile

Freud hypothesized that suicide is the result of an intrapsychic struggle between a cruel, punishing superego and an enfeebled, unloved ego (2). Menninger extended Freud's theory, describing suicide in a depressed person as the result of self-love turned to hate. The person then kills the despised object, himself (3). Proceeding further, Fenichel suggested that suicide may be an attempt to fulfil illogical wishes or desires, including the hope of rejoining someone already dead or following in the path of an admired person who has committed suicide. Thus, suicide is the symbolic killing of the critical superego with the hope of reuniting with a previously experienced pleasing superego (4).

To help develop an assessment of potential suicide risk for a particular patient, consider these psychopathologic mechanisms in conjunction with clinical data on suicidal patterns, in the form of a clinical profile adapted from Butler and Lewis (5) and including age and sex; early losses or trauma; diagnosis; history, current or past, of suicidal threats, notes, attempts to put affairs in order; depression; bereavement; isolation; physical illness: pain, diminished function; impaired cognitive functioning: dementia, alcohol/drug abuse; anticipation of death.

Age and Sex. In the United States, white men over 50 make up about 10% of the population and constitute 28% of all deaths by suicide. The rate

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for white women and blacks of both sexes is high in the later years but tends to peak in middle age (6).

Early Losses and Trauma. A person's early exposure to loss or trauma—particularly the loss of a parent and especially one's mother—may predispose to later hopelessness, depression, despair, and lack of will to struggle on (7).

Diagnosis. No matter how the study is designed, depression is the largest diagnostic category (about 50%) in those elderly who suicide (6). Depending on the population examined, drug abuse, organic brain disease, and psychosis comprise small percentages of the remaining half.

Suicidal History. Among the elderly, most first-time suicide attempters succeed. The ones who fail usually use so-called low-lethal methods (pills or wrist-cutting) rather than high-lethal methods (firearms, hanging, or jumping). A second attempt by whatever means is usually more lethal than the first.

Depression. Depression is quite frequent among older persons. About 30% of those over 65 will experience an episode of depression severe enough to interfere with daily life (8). Classical vegetative signs as well as the typical psychological symptoms are present. In addition, cognitive slowing, called "pseudodementia," is not infrequent.

Obviously, only a fraction of those who are depressed actually suicide. Researchers attempting to correlate which segments of the depressed are most at risk have hypothesized two subgroups: those whose wishes, hopes, or demands are impossible to achieve, and those whose depression contains a significant amount of anger (9).

Bereavement. An inescapable part of the aging process is the necessity of confronting both important losses and an ever-increasing number of losses. In the bereaved elderly, one finds more physical symptoms and a greater difficulty recovering from grief than in younger persons. The overwhelming sense of loss, physical manifestations of pain, chronic debilitation, and, frequently, associated hostility and guilt often lead to visits to physicians and to suicidal intent.

In the elderly, the risk of clinical depression and suicide is particularly great after the loss of a spouse. Depression occurs in about 20% of widows and widowers during the first year after the spouse's death (10).

The incidence of suicide after such a loss is highest within the first day or two (1). This is an impulsive suicide, prompted by denial of the reality of the loss, fear of living alone, and possibly a reunion fantasy.

The anniversary of a death is also a period of high risk.

Isolation and Withdrawal. Many elderly persons live alone, including those who have never married and many who have a substantial network of friends and prefer to live by themselves. However, another group, often widows or widowers, are not only isolated but feel "desolate"; they feel lonely and alone and are pained by it (9). It is this latter group that is of higher suicidal risk.

Cognitive Impairment. Elderly persons with diminished cognitive functioning, especially those who have concomittant depression, have been identified as having higher suicidal rates. The etiology of the reduced cognition includes senile and multiinfarct dementia as well as substance abuse.

Substance abuse in this age group can often begin innocently as over-the-counter medication, alcohol, or prescriptions for anxiety, pain, or sleeplessness. Those most at risk have a history of prior misuse (abuse) at a younger age.

Anticipation of Death. This group, who foresee the ending and have no hope of relief, is often thought to contain a high number of unreported suicides.

In sum, a combination of life losses (health, independence, loved ones) coexist with psychological factors such as self-hate and the fantasy of escape. This composite forms the descriptive profile of the potential suicide.

Management

Interview. Increased contact between physicians and their patients in the weeks and months prior to a suicide is known to take place (Table) (1). The symptoms are often multiple and nonspecific. Accordingly, one must meet every older patient with the thought of assessing their mental state

TABLE 1

Final Visits to Physicians by White Male Suicides 60 and Older in Maricopa County, Arizona, 1/1/71–6/30/75

Timing of final visit re suicide	No.	%	Cumulative %
Same day	1	3.23	3.23
One week or less before	9	29.03	32.26
One month or less before	13	45.16	77.42
One year or less before	3	9.68	86.66
More than a year before	4	12.93	99.99
Total	31		

Source: Adapted from Miller (1).

and level of psychosocial stress as well as their physical health.

While you are taking a history, the older individual is evaluating your skills and interest. They will focus on empathy, expressions of caring, and a sense of hope. Do you really try to understand? Will you listen to charged emotional material? Are you patient with their poor vision, diminished hearing, and slow responses? Do you make time to consider their fears of further loss of function?

In order to form a good working relationship, the physician is expected to be a caregiver in the broadest sense of the word.

Interviewing techniques necessary to assess suicidal risk include all those needed to obtain a good medical history: patience, empathy, a high index of suspicion, and the determination to do a thorough job. If you suspect a life crisis such as potential suicide, consider asking the following ten basic questions, assessing the crisis (11):

1. Why seek help now? Is there a crisis?
2. Tell me what caused this crisis?
3. Have you made an attempt to solve this crisis? Is it working?
4. How were you functioning before this crisis?
5. Is there any noticeable difference between then and now?
6. Has anything like this happened before?
7. How have you handled other similar situations?
8. Who are the people you can really rely on, no matter what?
9. Is this a long-term situation or a sudden, acute one?
10. Do you recognize the seriousness of your crisis?

The goal is to help develop a broad picture of the area of concern.

Supplemental History. To what extent should the examiner go directly to the person's support system to gather additional history? When the issue is potential suicide, the physician should openly discuss the need to inquire with significant others and do it in person or on the phone right at the moment. Often, the additional data is essential to planning.

Queries about Suicidal Thought. Caregivers commonly feel quite uncomfortable asking about suicidal thoughts. Whether from a personal bias or fear of activating an idea in someone's mind, this area of concern is often only cursorily questioned.

An appropriate approach is one of increasingly specific questions scattered throughout the interview, including these:

Have you hopes or plans for the future?
Do you expect to recover from your complaints?
Do you think about death?
Do you wish for death?
Have you ever planned to take your own life?
  If yes, please describe.
Have you ever attempted suicide?
  If so, please describe.

One must develop the patient's responses as clearly and completely as possible. The how, where, by what means, were the means available, when, where were those close to you, and what did you do afterwards elicit crucial data about the potential lethality. The discussion should be open and collaborative rather than adversarial.

When injuries or neglect are self-inflicted, one must acknowledge recognizing this fact to the patient. If one cares for the wounds or reinstitutes disregarded medications while leaving the associated suicidal issues unchanged or unresolved, the person is set free to act again.

Intervention

Suicide prevention is more accurately called suicide intervention. It is closely tied to recognition of potential suicides, followed by relieving the psychological, situational, and physical precipitants (12).

In-Patient Referral. Recalling that the ratio of suicidal attempt to fatal result in this age group approaches 1:1, those who have just made a gesture, written a suicide note, or completed specific preparatory plans are candidates for immediate psychiatric hospitalization. For this patient group, one would be remiss to allow oneself to be talked out of a safe and structured setting by the patient or concerned caregivers. An in-patient stay for evaluation and treatment is necessary.

A note of caution: the decision to seek hospitalization should be combined with absolutely constant monitoring of every movement until the patient is safely in the psychiatry unit itself. Any lapse of vigilance, no matter how brief, presents the actively suicidal person with one more chance to carry out the suicidal intent.

Out-Patient Management. It is obviously impossible and unwarranted to hospitalize all those elderly who are at risk but do not give specific indications. At the same time, it is clear that out-patient management of rather high-risk potentially suicidal patients is a difficult and emotion-filled task.

The physician often feels shocked or angry at the person's suicidal attitude or burdened by the sudden, immense responsibility (13). This reaction must be overcome in order to work effectively with such patients.

Caregivers must learn to listen to their own internal feelings of distress and discomfort. As a guideline, if you can't sleep because you are concerned about the patient's safety, a change in plans is necessary. You cannot effectively communicate control and hope if you yourself are too uncomfortable.

Help is always available. A colleague's opinion, a psychiatric consultation, or an emergency room psychiatric evaluation can be obtained. Most patients will cooperate with the referral if they know that you need it to more effectively continue with their care.

The patient is informed that you recognize their distress, that you are aware that they have serious questions about living, and that the two of you will act together, and immediately, to start resolving the distress.

Often the easiest and most immediate interventions create environmental changes: involving a family member or friend; or if that is not possible, perhaps hiring a companion or neighbor. Consequently, emotional support and help with personal and household care can be initiated. However, a person cannot be constantly watched at home. If such care is necessary, an in-patient setting is required.

Appropriate medications prescribed in small amounts with no initial refills can be helpful. Serum levels and toxicologic studies can be drawn at future meetings if suspicion of misuse or neglect is aroused.

Specific follow-up plans add strength to a sense of working together and to the expectation that the effort will be beneficial. All involved should agree to keep in contact frequently and openly by telephone and follow-up visits. Time should be set aside to talk.

The committment to see the crisis through should obviously be genuine. However, if cooperation becomes problematic or additional setbacks occur, plans to continue with out-patient supervision must be reevaluated.

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Serious Infections in the Elderly

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The fastest-growing segment of the population is the over-85 age group, which is projected to increase from 3% in 1980 to 14% in the year 2040 (1, 2). Although the elderly are generally believed to be particularly prone to infections, in fact, neutrophil production function and complement function, both the classical and alternative pathway, are normal (3). However, decreases in cell-mediated immunity and skin-test anergy are associated with aging (4). The number of T cells responding to antigens is decreased, and their response is altered (3, 5, 6). Depressed response to immunization has also been reported (7, 8).

Most believe that diseases associated with aging (diabetes, vascular disease, arthritis, neoplasia) are responsible for increased susceptibility to infection (3, 9, 10). Drugs associated with treatment of these syndromes, such as antineoplastic agents and corticosteroids, may further enhance that susceptibility (11, 12), as can such devices as indwelling urinary catheters, intravenous lines, or nasogastric and endotracheal tubes (13). Patients over the age of 60 accounted for 64% of all nosocomial infection (14); these infections are decade-specific, increasing from 10/1,000 in discharged patients aged 40–49 to 100/1,000 in discharged patients over age 70 (14).

This paper briefly approaches the problem of infections in the elderly from two aspects—the prevention of infection and the diagnosis and treatment of established infections.

Prevention

Pneumonia. The incidence of death from respiratory infections (influenza, pneumonia) is increased in the elderly (15). Influenza vaccination of elderly patients with heart and pulmonary disease and diabetes is strongly recommended, since mortality is associated with these risk factors and they are additive (15). Elderly persons without known risk factors should also be immunized, since the rate of complications, including pneumonia, hospitalization, and death, is decreased in the vaccinated group (16).

The elderly are also at increased risk of mortality when they develop serious systemic pneumococcal infection, including bacteremia and pneumonia (17, 18). Pneumococcal vaccination of the elderly is therefore recommended (19), but its efficacy in the aged is controversial. Two studies reporting on prospective trials have not shown a significant benefit (20); there was no significant reduction in frequency of systemic pneumococcal infection, pneumonia, or deaths from pneumococcal infection. However, two recent studies, using a different method of analysis (21, 22), suggest that the vaccine may be efficacious. The new 23-valent polysaccharide represents 87% of the bacteremic pneumococcal isolates reported by the Centers for Disease Control in 1981 (23). Further studies are pending, and when no contraindication exists, it seems prudent to immunize the elderly at greatest risk—those with underlying disease and those in nursing homes.

Community-acquired pneumonia in the elderly is caused by *Streptococcus pneumoniae* and a variety of other agents (24, 25). Gram-negative bacilli colonize the elderly pharynx proportionately more in those living in nursing homes and hospitals than in those living at home; in one study the overriding factors associated with such colonization were bedridden status and respiratory disease (26). Therefore, keeping patients active and out of bed, decreasing colonization, might also lower the incidence of pulmonary infection. The elderly have decreased pulmonary function, gag reflex, and mucociliary clearance, which may increase the risk of microaspiration, leading to pneumonia (25). But in the elderly

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mouse at least, the age-associated changes in bronchoalveolar function that do occur do not predispose the animal to lethal infection with common bacteria (27).

A variety of studies of community-acquired pneumonia have revealed an increase in infection with gram-negative bacilli, including *Hemophilus influenza* and *Escherichia coli, Acinetobacter sp,* and *Branhamella sp* (24, 25, 28, 29). Enterococcal pneumonia has been associated with nasogastric intubation (30).

Urinary Tract Infection. The prevalence of urinary incontinence varies from 5% to 20% among those living in the community (31, 32) and from 40% to 75% in among those in long-term facilities (33, 34). The rate of urinary tract infection is markedly increased in the elderly (35), as is the prevalence of bacteremia secondary to urinary tract infection; in fact, urinary tract infection is the most common cause of bacteremia in many facilities (35).

Indwelling urinary drainage catheters are also associated with bacteriuria (36) and bacteremia; even the condom catheter, once believed to be infection free, is associated with high rates of infection (37). Nosocomial spread of urinary tract isolates from patient to patient most often occurs secondary to poor infection control practices (38). The failure of hospital staff to exercise caution by simple hand washing often increases the spread of those isolates between patients. In nursing homes, low levels of education of most nonskilled staff (39) and lack of infection control procedures have further increased the dimension of this problem. The use of prophylactic antibiotics has been deleterious, since they select for multiple resistant strains. In-house education programs directed to all staff levels, as well as improved nursing-home infection control guidelines, may prove beneficial.

Skin. With advancing age the structure of the skin, the largest organ in the body, is deleteriously affected. Thinning of all layers and dryness occur (39, 40). This, coupled with a decrease in the Langerhans cells (immunocompetent skin cells), puts the patient at risk for infection (41). Superficial cracks in the skin are often associated with cellulitis, lymphangitis, abscess, and occasionally the more severe fasciitis. The diabetic and the patient with neurovascular disease are more prone to anaerobic organisms, which flourish in areas with low oxygen supply. Other common organisms often associated are *Streptococcus pyogenes* and *Staphylococcus aureus* strains.

The skin is one of the most common sources of bacteremia in patients with *S. pyogenes* infections. In one study, the elderly developed severe necrotizing skin infections from *S. pyogenes;* the hospital staff had mild pharyngitis when infected with the same organism (42). The skin may be the source of *S. aureus* or *S. epidermidis* strains isolated in the elderly with infective endocarditis; therefore, skin care should be taught elderly patients with diabetes and vascular disease. The use of skin moisturizers may be significant in this regard though further studies are necessary for verification.

Soiling the perianal area may increase the rate of skin breakdown and subsequent development of infected decubiti. Decubiti in the immobilized elderly are often associated with concurrent infection. The isolates are usually mixed, including gram-positive and gram-negative aerobes and anaerobes (43), and bacteremia, often polymicrobial, is associated. Attempts at cure require appropriate antibiotic therapy and aggressive surgical debridement to prevent further necrosis and often forestall death from septicemia. Obviously, skilled nursing care to prevent pressure sores will forestall this development.

Tetanus, a rare but often fatal disease, especially in the elderly, is entirely preventable. In one study from England, one-third of elderly patients who acquired tetanus did so following gardening injuries (44). In many patients there is no wound to implicate, despite the widespread notion that puncture wounds are always the cause. In fact, many of these infections occur indoors. Many elderly have never received primary tetanus immunization and are at increased risk (45, 46). It is important to question patients at the time of injury as to their immune status; if it is unknown, therapy with tetanus immune globulin and tetanus toxoid should be administered (the same site should not be used for both injections).

Endocarditis or Prosthetic Device Infection. A variety of manipulations and normal body functions have been associated with bacteremia, including chewing, defecation, and dental manipulation. Intubation as well as gastrointestinal procedures such as endoscopy, sigmoidoscopy, barium enema, and genitourinary manipulation are also associated (47). The bacteremia usually is short lived, occurring within 30 min to 1 hr after the procedure; most often streptococcal organisms are isolated (47). The number of bacteria isolated in the bloodstream following tooth brushing (20–200/ml) is equal to that reported after dental manipulations (47). It is, however, strongly recommended that antibiotic prophylaxis be given to certain high-risk groups, which include patients with valvular and congenital heart disease and arteriosclerotic heart disease and those with prosthetic valves before dental and other procedures (48, 49). The American Heart Association has recently revised its guidelines for these high-risk groups, who may undergo dental, genitourinary, or other procedures (50). The recommendations are not founded on hard science but rather on animal experiments, which clearly do not exactly mimic the human situation (47). Given the litigious environment we exist in, it seems prudent to observe these guidelines, especially in persons with valvular disease undergoing either dental or genitourinary manipulations. Whether to give prophylaxis before the administration of a barium enema has not been determined. Patients with other prostheses—hip, knee, ocular, vascular grafts—may constitute another group at risk. Bacteremia, especially from staphylococci and streptococci, could present serious hazards. Whether these organisms will implant and cause subsequent infection is not known. Similarly, it is not known whether antibiotic prophylaxis will prevent implantation or whether toxicity from these antibiotics will increase the risk-benefit ratio, especially in the elderly. Each patient should be evaluated individually.

Diagnosis and Management

Community-Acquired Pneumonia. In patients suspected of having bacterial pneumonia because of classical symptoms or failure to thrive, or positive chest radiograph, attempts at defining etiology are necessary. A number of studies have revealed the difficulties with sputum cultures and smears (51). For some clinicians only positive transtracheal aspirates, pleural fluid cultures, or hemoculture is considered significant to define etiology. Transtracheal aspiration is not without known complications (51). When patients are admitted from an extended-care facility or adult residence, the possibility that gram-negative bacteria may be causal agents must be considered. Following appropriate laboratory tests, when the etiology is not known, the therapy could begin with an antibacterial agent (a second-generation cephalosporin) that covers the most likely community pathogens (*S. pneumoniae, H. influenzae, S. aureus, Klebsiella sp*). Because cefuroxime penetrates into the meninges, it may afford the clinician an extra margin of safety. Whether other gram-negative bacilli such as *E. coli, Pseudomonas sp,* and *Acinetobacter sp* will increase in frequency is unknown; if they do, perhaps a third-generation cephalosporin, with expanded spectrum, will be necessary. Specific as opposed to broad-spectrum therapy should be substituted when appropriate cultures are found.

Nosocomial Pneumonia. Nosocomial pneumonia is associated with a greater mortality in the elderly (14). The most common pathogens isolated from the lower respiratory tract on both medical and surgical services in the 1983 National Nosocomial Infection study, which represented over 60 hospitals, were gram-negative bacilli: *Pseudomonas, Klebsiella sp,* and *S. aureus* (52). In hospitalized patients exact diagnosis is the most difficult because oral-pharyngeal colonization with gram-negative bacilli is greater (26). Therapy with agents directed against these pathogens seems prudent—either third-generation cephalosporins alone or in combination with an aminoglycoside or a combination of expanded spectrum penicillins, or cefazolin coupled with an aminoglycoside. Monotherapy of gram-negative pneumonia with the newer beta-lactam agents has been carried out in order to avoid aminoglycoside toxicity. Ototoxicity from aminoglycosides is greater in the elderly (53); even pretherapy audiograms are reported to be abnormal in 75% of hospitalized patients (54, 55). Netilmicin, a newer agent, is reported to have decreased ototoxicity and may offer some advantage in this age group (56). In patients with pneumonia treated with either gentamicin, tobramycin, or amikacin, clinical outcome correlated with increased serum levels greater than 6 μg/ml for tobramycin and gentamicin and 24 μg/ml for amikacin (57); however, increased serum levels of aminoglycosides may correlate with nephrotoxicity and ototoxicity (53). Thus, whether monotherapy or combination therapy is selected will depend on individual clinical judgment, keeping in mind the potential toxicity of these latter agents.

Bacteremia. In the elderly patient, bacteremia may be more subtle, sometimes occurring without fever (58). In a study of pneumococcal bacteremia, 29% of patients were afebrile (57). Signs of confusion, decreased mentation, diarrhea, falling, and unexplained hypotension may be significant clues to sepsis. The urinary tract is the most common source of both community- and hospital-acquired bacteremia (13, 60, 61). In the hospital setting, if the urinary tract is suspected, then use of agents with coverage of gram-negative bacilli is appropriate, such as potent cephalosporins or expanded-spectrum penicillins.

If the skin is a suspected source, use of agents with efficacy against penicillin-resistant *S. aureus* is mandatory; coverage should also include *Strep. pyogenes;* both are common organisms causing cellulitis, lymphadenitis, fasciitis, and bacteremia. If a source, either an abscess or indwelling catheter, is found, drainage and removal are often necessary.

In one long-term care facility, 67% of patients with gram-negative bacteremia had an associated 25% mortality, and 24% with gram-positive bacteremia had an associated 50% death rate. With polymicrobial bacteremia the death rate was 67%. The source was the urinary tract in 56% of the cases (60). If the source of sepsis is unknown, broad-spectrum antibiotic therapy is warranted. Overall, the most frequent isolates causing bacteremia reported in the 1983 nosocomial study were coagulase-negative staphylococci 14.2%, *S. aureus* 12.8%, *E. coli* 9.5%, *Klebsiella spp.* 9.1%, and enterococci 7.3% (52).

Endocarditis. This syndrome may occur with only subtle signs of infection in the elderly. Clinical suspicion in a patient with fatigue, lassitude, and night sweats with or without fever should mandate blood cultures even in patients without valvular disease or heart murmurs (59). Group D streptococci such as *S. faecalis,* especially in patients with history of either genitourinary tract infection or tract manipulations, should be considered. In this case combination therapy with either penicillin or ampicillin plus an aminoglycoside is necessary. *S. bovis,* a nonenterococcal group D isolate, has been associated with colon carcinoma and other gastrointestinal lesions. Investigation of the bowel is prudent when this organism is isolated (62).

Endocarditis should be also suspected in any patient with neurologic symptoms and signs associated with either a heart murmur or fever. In patients with negative blood cultures, a diagnosis of nonbacterial thrombotic endocarditis and atrial myxoma should be entertained. A diligent search for an underlying malignancy is called for in patients with nonbacterial endocarditis.

Genitourinary Tract. In patients with either prior urinary tract infections or indwelling drainage catheters, bacteremia is more common. As reported in the National Nosocomial Infection Surveillance Study, the most common isolates in the hospital setting causing urinary tract infections were, in order of decreasing frequency, *E. coli* 31.7%, enterococci 15%, *Pseudomonas aeruginosa* 12.5%, *Klebsiella sp* 7.6%, and *Proteus sp* (52). Opinion on whether to treat patients with bacteriuria with indwelling drainage catheters is divided (63). Therapy was not better than observation in one study (63); resistant organisms may be selected after therapy is stopped. However, in patients with systemic symptoms, chills, or fever, therapy is mandatory. In patients with isolates of antibiotic-sensitive organisms who fail to respond, a careful search for obstruction secondary to stone, malignancy, or prostatic or renal abscess must be performed. Patients who subsequently develop back pain may have vertebral osteomyelitis, which in this age group often follows genitourinary tract infection. Vertebral osteomyelitis may also occur without prior history of genitourinary infection. In fact, in any patient with fever of obscure origin, this diagnosis should always be considered.

Nosocomial spread of infection to nearby patients often involves urinary tract infection and catheter drainage. Infection control practices should be taught and observed by staff caring for these patients.

Meningitis. *S. pneumoniae* and gram-negative bacilli may cause meningitis in the aged (64, 65). *Listeria monocytogenes, H. influenzae,* and group B streptococci are also isolated in elderly patients. Symptoms may be explosive; sequelae and death are more common in the elderly. Therapy with cefuroxime, cefotaxime, and ceftriaxone is effective, as is penicillin for sensitive isolates. However, *L. monocytogenes* should be treated with ampicillin plus an aminoglycoside.

Gram-negative bacillary meningitis may be indolent in the elderly. Clinical suspicion based on mental changes, even in the absence of a stiff neck, requires a spinal puncture. Spinal fluid findings may reveal only a paucity of polymorphonuclear leukocytes, and the gram stain may be negative. Therapy with potent agents such as cefotaxime, ceftazadime, or ceftriaxone has been associated with clinical efficacy. Even so, older patients with meningitis have increased risk of complications, such as pneumonia, seizures, neurologic deficits, and a higher mortality (65). Tuberculous meningitis should be considered when routine cultures are negative and the clinical findings are otherwise unexplained (66).

Septic Arthritis. Septic arthritis in the elderly should be aggressively treated. It is most often recognized in patients with a prior history of osteoarthritis and rheumatoid disease (67). Failure to make the diagnosis may lead to further articular changes and to death. Pathogens isolated in one study were *S. aureus* (50%) and gram-negative bacilli 30% (67). The increase in gram-negative bacillary isolates is consistent with their isolation from other sources in the elderly.

Aspirations or surgical drainage combined with antibiotics are required. Since most antimicrobial agents penetrate into the joint fluid, intraarticular antibiotics are not necesary and may even be toxic to the articular surface. Following diagnostic procedures such as joint aspiration, initial therapy with cephalosporins with activity against *S. aureus* should be initiated. Gram stain and culture are necessary. Antipseudomonal agents alone or in combination may be necessary if the cultures are positive for this isolate.

Miscellaneous Infections. Conjunctivitis, especially in nursing homes, is common (28). Local therapy should be initiated if a bacterial source is identified. A recent case due to *Nisseria gonorrhea* was seen by the author in a 67-year-old woman who apparently shared a towel with a house guest who had gonococcal urethritis; careful investigation of these patients by gram stains and culture is necessary to prevent loss of vision from virulent pathogens.

Malignant external otitis is an infrequent but serious infection in the elderly diabetic; in our series 10/11 patients were more than 65 years of age (68). Awareness of the association of ear drainage and otalgia in a diabetic necessitates aggressive antimicrobial therapy for *Pseudomonas aeruginosa* and surgical debridement.

Food Poisoning. Outbreaks of bacterial gastroenteritis caused by *Salmonella sp* and *Shigella sp* in long-term facilities caring for the elderly are often associated with mortality higher than in the general population (69). Recent outbreaks of milk contaminated with both *Listeria sp* (70) and *Salmonella sp* (71) as well as prior outbreaks (72, 73) point up the need for diligence in diagnosing and treating those elderly patients. Following stool smears and culture, careful attention to fluid balance is required. Although antimicrobial therapy is not indicated in most normal adults (74), it seems prudent in those elderly patients who are more severely ill. Trimethoprim/sulfamethoxazole is a useful agent in cases of proven *Shigella* infections; treatment of *Salmonella sp* is often required for the elderly with systemic symptoms.

Summary

The disease states associated with aging—neoplasia, cardiovascular disease, and diabetes—and medicines administered are the most likely factors leading to both an increase in infections and subsequent difficulty in recovery. Prevention of infection therefore must be the first step. Immunization for viral influenzae A and B is recommended for those with underlying disease and residents of nursing homes. Immunization for *S. pneumoniae* should probably be given to those with known risk factors. Since immobilization is associated with increased colonization and pneumonia, physical therapy and rehabilitation should be carried out in nursing homes. Infection control programs, primarily in nursing homes, may further prevent cross-infection from patient to patient.

Since the elderly may not have classical signs of infection such as fever, any change in behavior or mental state and failure to thrive should be viewed with suspicion. Following appropriate cultures and laboratory tests, swift, judicious antimicrobial administration may prove beneficial in decreasing mortality in this group. It is difficult and sometimes impossible to differentiate gram-positive from gram-negative infection. Beta-lactam drugs, with their broad antibacterial spectrum, excellent pharmacokinetics, tissue distribution, and lack of toxicity, appear to be the empiric agents of choice. When the clinical situation deteriorates, judicious addition of aminoglycosides is warranted. In order to determine rational antibiotic therapy, knowledge of pharmacokinetics of antibiotics in the elderly must be considered. Renal and hepatic function is most often decreased in the elderly despite normal laboratory values (75, 76), usually necessitating a lower dosage and increased dosing interval. Newer, still experimental agents including mono-bactams and the quinolones may add further to efficacy without increasing toxicity.

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Emergency Surgery in Patients Aged over 70 Years

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Abstract

Our review of all general surgical procedures at the Mount Sinai Hospital performed in one year in persons over 70 showed that in 100 patients who required emergency surgery, morbidity was 31% and mortality 20%—significantly greater than the 6.8% morbidity ($p < 0.0005$) and 1.9% mortality ($p < 0.0005$) in 513 patients of the same age group who underwent elective procedures during the same interval, Nov. 1, 1983 through Oct. 31, 1984. Infection was the most common indication for urgent operation (28%), followed by intestinal obstruction (25%), incarcerated hernia (17%), and hemorrhage (13%). The majority of complications were related to the cardiopulmonary systems; 80% (16/20) of deaths occurred from multisystem failure in the intensive-care unit. No correlation was found between increasing age and morbidity or mortality. We believe that improvement in medical care of the elderly will come not from technologic advances but from better understanding of their social conditions and biologic capabilities.

The elderly constitute an increasing portion of the global population (1). In the United States in 1984 12.1% of the inhabitants were over the age of 65. The Census Bureau projects the group will increase to 13.1% of the population by the end of the millennium (2). Only recently have the unique medical needs of this large group been recognized and addressed.

We have been distressed by the number of aged patients whose cases are discussed at weekly morbidity and mortality rounds. We therefore undertook a review of all general surgical procedures in persons over 70 in order to identify the relative frequency of surgical diseases and to document operative complications. This report is an analysis of emergency operations performed on our geriatric patients.

Materials and Methods

A retrospective study of all procedures performed at The Mount Sinai Hospital, New York, on the general surgical services from November 1, 1983 through October 31, 1984 was conducted. Information on operative procedure, duration of surgery, age, gender, and length of hospitalization was obtained from the operating room computerized database and the Department of Medical Records. Patients who were over age 70 years and who underwent intraabdominal or abdominal wall operations were included. Emergencies were defined as those cases that could not wait for the next scheduled operating room time.

Morbidity and mortality statistics were culled from the weekly reports submitted by the senior surgical resident on each of the three general surgical teams. The charts of those patients were reviewed for further details. Complications were listed individually when possible. Many patients, however, sustained insults to more than one organ system. In such instances patients were grouped under the heading multisystem failure.

Statistical analysis was performed with Student's t test for independent samples utilizing pooled variances. Counted data were evaluated with the chi-square test incorporating Yates' continuity correction. Means are given ±1 SD. The

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TABLE 1
Indications for Emergency Surgery in Patients >70 Years

	No. cases		No. cases
Obstruction	25	**Perforation**	10
Gastric	3	Duodenum	3
Small bowel	13	Stomach	3
Large bowel	9	Small bowel	2
		Large bowel	2
Infection	28	**Hemorrhage**	12
Diverticulitis	5	Upper	9
Appendicitis	6	Lower	3
Cholecystitis	11		
Abscess	6	**Hernia**	17
Ischemia	5	Inguinal	14
Small bowel	3	Umbilical	3
Large bowel	2	**Other**	5
Total		102	

TABLE 2
Emergency Procedures in Patients >70 Years

	No.	Morbidity	Mortality
Colon	25	6	3
Abdominal wall	17	1	0
Gastric	17	11	7
Biliary tract	11	2	1
Small bowel	10	5	5
Abscess	6	2	1
Appendix	6	0	0
Adhesions	5	1	0
Other	5	3	3
Total	102	31	20

TABLE 3
Morbidity Associated with Emergency Surgery in Patients >70 Years

	No.		No.
Arrhythmia	1	Anastamotic leak	1
Myocardial infarct	2	Wound infection	1
Congestive heart failure	1	Cerebrovascular accident	1
Pneumonia	1	Duodenal stump leak	1
Dehiscence	1	Incidental splenectomy	3
Evisceration	1	Multisystem failure	16
Abscess	3	Upper GI bleed	3
Common bile duct injury	1	Respiratory failure	2
Total		39	

coefficient of correlation was calculated according to Pearson; p values <0.05 were sufficient to reject the null hypothesis.

Results

During the study interval, 676 intraabdominal and abdominal wall operations were accomplished in 613 patients older than age 70. Fifteen percent (102/676) were performed as emergencies. Patient ages ranged from 70 to 95 years, with a mean of 78.9 years ± 6.4 years. Septuagenarians constituted 55% (55/100), octogenarians 39% (39/100), and nonagenarians 6% (6/100) of the study group; 62 patients were women and 38 were men.

Emergency surgery (Tables 1, 2) was associated with 31% morbidity and 20% mortality, significantly greater than the 6.8% (39/574) morbidity ($\chi^2 = 46.4$, $p < 0.0005$) and 1.9% (11/574) mortality ($\chi^2 = 60.5$, $p < 0.0005$) following elective operations in the same age group. This was also significantly greater than the 14% (30/215) morbidity ($\chi^2 = 10.1$, $p < 0.005$) and 6.0% (13/215) mortality ($\chi^2 = 11.0$, $p < 0.001$) associated with emergency surgery in patients under age 70.

Thirty-one operations were followed by 39 complications (Table 3). The mean age of these patients was 77.5 years ± 7.1 years. There were 9 men and 22 women; they occupied a total of 345 intensive-care bed days (mean 12.8 days ± 13.7 days). The 20 deaths occurred 10.5 days ± 11.8 days postoperatively. No correlation was found between increasing age and morbidity ($r = -0.04$) or mortality ($r = -0.05$).

Obstruction. Thirteen patients had symptoms of small-bowel obstruction. Adhesions were responsible for 11 cases. Six required small-bowel resections in addition to lysis of the obstructing band. Two patients underwent right hemicolectomy for obstructing cecal carcinomas.

Large-bowel obstruction secondary to carcinoma was the indication for 6 colostomies and 1 left hemicolectomy. One patient underwent a subtotal colectomy for pseudoobstruction, and another patient had an ileocolic bypass for obstructing metastatic carcinoma.

Gastric obstruction was present in 3 patients. One had an incarcerated diaphragmatic hernia and underwent reduction and repair. Another patient had a pancreatic neoplasm and underwent gastroenterostomy. The third patient had an obstructing gastric tumor and underwent subtotal gastrectomy.

Infection and Inflammation. Five sigmoid resections and Hartmann procedures were performed for diverticulitis. Eleven patients underwent cholecystectomies, of whom 4 had concomitant common bile duct exploration. Six patients required appendectomies. Six abscesses were drained, 4 intraperitoneal and 2 extraperitoneal.

Incarcerated Hernia. Fourteen inguinal and 3 umbilical herniorrhaphies were performed. Strangulated bowel was discovered in 1 patient in each group necessitating small-bowel resection.

Hemorrhage. Upper-gastrointestinal hemorrhage was responsible for 9 emergency procedures. Four patients underwent plication of duodenal ulcers in conjunction with a vagotomy and drainage procedure. One required a Billroth II procedure for recurrent bleeding. Three patients had gastric ulcers, of whom 1 underwent simple plication, another local resection, and the third subtotal gastrectomy. An esophagogastrectomy was performed for therapy of a gastroesophageal junction ulcer.

Three patients required colon resections for control of hemorrhage. One was bleeding from a cecal angiodysplasia, and the second had an ileocecal artery aneurysm. Both underwent right hemicolectomies. A left-colon resection was performed for bleeding sigmoid diverticuli.

Ischemia. Five patients were operated on for intestinal ischemia secondary to atherosclerotic disease. Two patients had extensive small-bowel resections and another an exploratory celiotomy to establish the diagnosis. One patient underwent right hemicolectomy, and a subtotal colectomy was performed on the remaining patient.

Perforation. Duodenal and gastric ulcers were each the cause of 3 perforations. Two patients with duodenal ulcers underwent plication alone, and 1 had the perforation incorporated into a pyloroplasty. Plication was performed for 2 perforated gastric ulcers, and a Billroth II gastrojejunostomy was accomplished in the third.

Two patients underwent small-bowel resections following perforation of obstructed bowel. Two iatrogenic colonoscopic perforations necessitated laparotomy. One patient required a left hemicolectomy, and the second had suture repair of a sigmoid laceration.

Other. Toxic megacolon in a patient with ulcerative colitis was the indication for a subtotal colectomy. Two patients underwent colostomy for diversion of stool from the rectum. Two exploratory celiotomies were undertaken for diagnosis and therapy of the acute abdomen. The first patient was found to have spontaneous bacterial peritonitis, and in the second no pathology was identified.

TABLE 4
Incidence of Emergency Procedures in Patients >70 Years

Operation	Ryan, 1955–1958	Blake, 1969–1975	Keller, 1983–1984
Colon	24%	23%	25%
Hernia	24%	32%	17%
Gastric	24%	14%	17%
Biliary	2%	6%	11%
Appendix	9%	9%	6%
Adhesions	4%	8%	11%
Other	13%	8%	13%

TABLE 5
Mortality Rates, General Surgical Procedures in Patients >70 Years

Author/Interval	Mortality	No. pts
Keller 1983–1984	20%	100
Ryan 1955–1958	29%	123
Herron 1955–1958	25%	205
Young 1966–1969	24%	50
Blake 1969–1975	32%	375
Palmberg 1964–1974	37%	—
Greenburg 1972–1979	20%	65

TABLE 6
Length of Hospital Stay, Emergency vs Elective Operations, in Patients >70 Years

	No. EM/EL*	Postop stay (days)
Right hemicolectomy	5/36	39.0/12.3**
Cholecystectomy	7/41	24.0/11.5**
Herniorrhaphy	14/141	8.9/5.0**

* EM, emergency; EL, elective.
** $p < 0.05$.

Discussion

The morbidity and mortality rates in elderly patients undergoing emergency surgery are truly alarming. The magnitude of the problem surpassed our initial estimates and has demonstrated that in spite of technologic improvements and surgical advances, emergency operation in this age group is fraught with danger. Health in the aged appears to be precariously balanced; one illness is capable of initiating a cascade of system failures, frequently resulting in death.

The decline of bodily functions with age has been well documented. The lungs demonstrate a net decrease in total volume and compliance (3). Cilia decrease in number and ability to function (4). Cardiac output and the ability to tolerate exercise decrease (5, 6). Thermoregulatory mechanisms are impaired (7), as are renal filtration and excretion (8). The elderly patient is thus poorly suited to withstand the stresses imposed by catastrophic illness and emergency surgery.

Despite an emphasis on preventive medicine and creation of social programs that provide the elderly population with access to medical care, the last three decades have witnessed neither change in the incidence of emergency surgery among patients in this age group who require surgery (9, 10) nor major alterations in organ system disease (Table 4). In addition, we seem unable to alter substantially the 20%–37% mortality that has persisted during the past 30 years (9–12) (Table 5). We therefore need to redouble our efforts toward disease prevention. When this fails, early detection and treatment must be our goal.

Operations performed electively were associated not only with decreased morbidity and mortality, but also with diminished consumption of hospital resources (Table 6). The cost of an emergency inguinal herniorrhaphy is illustrative. Urgent herniorrhaphy in the elderly represented 2.3% (14/602) of inguinal herniorraphies performed at our institution. These patients spent an average of 3.9 more days in hospital than their elective counterparts. Per diem charges are approximately $400. Extrapolation of this data to the estimated one million herniorrhaphies performed yearly in the United States (13) indicates that urgent herniorrhaphy in the elderly generates an additional expenditure of $11.6 million. Similar calculations for right hemicolectomy yield $19 million, and for cholecystectomy, $55 million.

We believe that substantial improvement in the care of our aged population will not result from advances in supportive technology, but rather from a better understanding of their sociologic condition and biologic capabilities. Both physicians and laymen must respond to the health needs of the elderly with the same thoroughness demonstrated for younger patients. Symptoms cannot be ignored, nor elective procedures unnecessarily postponed. The cry of the psalmist in Psalm 71 must be heard: “Cast me not off in the time of old age; forsake me not when my strength fails me.”

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Acute Appendicitis in Hospital Patients Aged Over 60 Years, 1974–1984

STEVEN B. HIRSCH, M.D. AND JOSEPH R. WILDER, M.D.

Acute appendicitis is a prototype of all nontraumatic surgical emergencies. Delayed hospitalization and treatment can lead to increased morbidity and even mortality. The elderly patient cannot tolerate the complications that misdiagnosis and preoperative delay often lead to. This study was undertaken to assess the differences between acute appendicitis in the elderly patient and acute appendicitis in the young adult and how these differences can be generalized to other surgical emergencies in the elderly patient.

It is well known that the geriatric population has increased dramatically over the past century. This shift in the age of the American patient has led to a sevenfold increase in the number of cases of appendicitis in the elderly over the past thirty years (1). In addition, U.S. statistics show that of the 1,397 deaths in patients with acute appendicitis, 63% occurred in patients sixty years or older (2).

Ryden (3), among others, has documented a significantly higher perforation rate in the elderly with acute appendicitis. He found a linear rise in perforation from the third to the ninth decade of life. Prior studies, however, have failed to elucidate the primary cause of this high perforation rate in the elderly. Many authors (3–8) have documented elderly patients' delay in seeking medical care. Others (9) have implicated physician delay in making the correct diagnosis and providing prompt surgical treatment. Peltokallio and Jauhianinen (10) found no difference in the duration of symptoms between the elderly and the younger adult. Others (11, 12) hypothesized that atherosclerotic reduction in blood supply, intraluminal narrowing, obstruction due to previous inflammation, and structural weakness of the wall may predispose to early perforation. The high perforation rate in the elderly with appendicitis and the controversy regarding its etiology form the basis for this study.

Methods

A retrospective chart review study of patients at The Mount Sinai Hospital between 1974 and 1984 with a discharge diagnosis of acute appendicitis was undertaken. Using the PAS computerized system which is organized by discharge diagnosis, random samples of patients aged 20 to 60 and patients over the age of 60 were obtained. The "pediatric" population, defined at The Mount Sinai Hospital as "birth to age 20," was not included because of altered clinical presentation. A study group of 70 patients aged over 60 years and 56 patients aged 20 to 60 was thus constituted. The charts of each of these patients were reviewed. Data was obtained from the emergency room sheet, the senior surgical resident's admitting note, the postoperative note, and the pathology report. Statistical analysis was performed using chi-square tests with Yates connection factor where appropriate.

Results

There were 1,735 cases of acute appendicitis (Table 1) at Mount Sinai between 1974 and 1984. The incidence of this disease has remained stable over the past decade. Patients over 60 years of age accounted for 10% of the total. In the last two years of the series, 1983 and 1984, 12.1% and 13.5% of the patients were over 60 years of age.

In the 1,272 cases of nonperforated appendicitis, there was only one death (mortality rate

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TABLE 1
Acute Appendicitis at The Mount Sinai Hospital 1974–84

Year	Total cases	60+ yrs No. (%)
1974	192	18 (9.4)
1975	180	22 (12.3)
1976	177	19 (10.7)
1977	145	15 (8.5)
1978	158	18 (11.4)
1979	132	6 (4.5)
1980	195	26 (13.3)
1981	185	11 (5.9)
1982	159	12 (7.5)
1983	116	14 (12.1)
1984*	94	13 (13.5)
Total	1,735	174 (10.0)

* 1/84–6/84

TABLE 2
Mortality in Acute Appendicitis at The Mount Sinai Hospital 1974–84

	Total cases	Mortalities No. (%)
Status		
Perforated	463	6 (1.3)
Nonperforated	1,272	1 (0.08)
Age		
60+ yrs	174	4 (2.3)
<60 yrs	1,561	3 (0.2)
Total	1,735	7 (0.4)

TABLE 3
Mortalities in Acute Appendicitis at The Mount Sinai Hospital 1974–84

Sex/ Age	Admitting Dx	Appendix	Complications
F/60	Metastatic colon ca	Perforated	
F/84	Intestinal obstruction	Perforated	Acute MI
F/93	Intestinal obstruction	Perforated; generalized peritonitis	Cardiopulmonary arrest
M/94	Incarcerated inguinal hernia	Perforated; generalized peritonitis	Bleeding gastric ulcer Pulmonary embolus
M/newborn	Difficult labor with birth injury	Perforated	
F/35	PID	Perforated	Acute CVA
M/47	Acute appendicitis	Nonperforated	Thrombophlebitis

0.008%). In the 463 cases of perforated appendicitis, there were six deaths (mortality rate 1.3%, or sixteen times that of nonperforated appendicitis) (Table 2). The mortality rate of those over 60 years was ten times that of those 20 to 60 years of age.

A closer look at the seven deaths revealed that three of the seven patients were aged 84, 93, and 94 (Table 3). This suggests that the population over age 80 may account for the majority of deaths. In addition, six of the seven were initially misdiagnosed, emphasizing the importance of prompt and accurate diagnosis.

The study group of patients over age 60 had less nausea (63% vs 89%), less vomiting (44% vs 67%), and more constipation (38% vs 26%) than the control group. Only vomiting and constipation proved to be statistically significant (Table 4).

The physical findings showed that 86% of controls and 77% of the study group had localized RLQ tenderness, a critical physical finding. However, 74% of the younger adults had rebound and rectal tenderness, indicative of peritonitis, whereas only 51% of the older patients did. A higher percentage of the younger patients displayed guarding (81% vs 66%), though this was not statistically significant. An interesting and statistically significant finding was the high percentage of elderly patients with abdominal distention (63% vs 40%). A somewhat higher percentage of the elderly also had an abdominal mass (22% vs 13%), most likely due to a higher percentage with appendiceal abscess. Both groups had a very high percentage of patients without tachycardia and without fever (Table 4).

The white blood cell count was a quite sensitive indicator of acute appendicitis in the study. Only 2% of the controls and 3% of the elderly had neither an elevated count nor a left shift in the differential. The elderly patients mounted leukocytosis as frequently and as high as the younger adult patients (Table 5).

The hospital stay and complication rate was significantly higher in the elderly. The average stay (17.0 vs 9.3 days) and the complication rate (37% vs 18%) were approximately twice as high in the elderly (Tables 6, 7).

The most important statistic was a perforation rate more than doubled in the elderly (68% vs 34%). The percentage with abscess formation was also doubled in the elderly (30% vs 16%) (Table 8). In a search for the etiology of this surprisingly high perforation rate, the duration of symptoms prior to presentation for medical care and the length of time between emergency room admission and surgery were examined (Table 9). The study reveals that the elderly delay seeking medical care and that physicians delay treatment of the elderly: 43% of the patients over age 60 waited more than 48 hours with symptoms before seeking medical attention, whereas only 18% of the younger adults waited that long. Forty-two per cent of the elderly patients were hospitalized for over 13 hours prior to appendectomy, whereas only 20% of the younger adults waited that long (Table 9).

Discussion

Many authors have documented the difficulty in diagnosing the acute abdomen in the elderly. Intraabdominal processes in the elderly are often associated with a paucity of symptoms and physical examination findings (1, 4, 23). Peltokallio and Jauhianinen (10) as well as Goldenberg (24) found no differences in symptoms or physical findings between elderly and younger adult patients. Goldenberg (24) believes that since the elderly generally have a twofold increase in perforation, they should have more severe symptoms and more impressive physical findings.

Yusuf and Dunn (13) stress the fact that the elderly often have had past abdominal surgery, which leads to an increased incidence of small intestinal obstruction, and that other intraabdominal conditions are more common in the elderly. This may confuse the physician in making the correct diagnosis and may confuse the patient in recognizing the possibility that a new life-threatening intraabdominal condition is present.

Hubbell et al (14) showed that the elderly displayed a greater incidence of normal WBC counts, which contradicts the findings of this study. Albano et al (15) found a higher mortality rate in those without leukocytosis, illustrating the danger of overreliance on any single laboratory value.

Virtually every study (2, 4, 13) has demonstrated a higher morbidity and mortality rate in elderly patients with acute appendicitis. Freund and Rubinstein (16) reviewed the collected series of appendicitis in the elderly. They found an alarmingly high mortality rate of 7.9%, complication rate of 40%, and diagnostic error rate of 21.6%. They also found the mean perforation rate in the elderly to be 57%. This data does not differ significantly from the data in this study, except for a lower mortality rate of 2.3% at The Mount Sinai Hospital. This may be attributed to safer anesthesia, broader use of invasive monitoring, and improved intensive care facilities.

TABLE 4

Acute Appendicitis in the Elderly Population at The Mount Sinai Hospital 1974–84

	Controls 20–60 yrs (N = 56)	60+ yrs (N = 70)
Symptoms		
Abdominal pain		
RLQ	77	63
Other	23	34
No pain	0	3
Nausea	89	63
Vomiting*	67	44
Anorexia	95	87
Constipation*	26	38
Diarrhea	22	22
Physical exam		
Abdominal tenderness		
RLQ	86	77
Other	12	17
None	2	6
Rebound tenderness*	74	51
Rectal tenderness*	74	51
Guarding	81	66
Abdominal mass	13	22
Rectal mass	6	6
Abdominal distention*	40	63
Bowel sounds		
Decreased	49	58
Normal or increased	51	42

* $p < 0.025$

TABLE 5

Acute Appendicitis in the Elderly Population at The Mount Sinai Hospital 1974–84

	Controls 20–60 yrs (N = 56)	60+ yrs (N = 70)
Tachycardia (pulse 100)	30	34
Temperature		
<100°F	48	34
100–101°F	39	51
>102°F	13	14
Average	99.9°F	100.2°F
WBC count		
<10000	12	13
10–20000	79	76
>20000	9	11
<10,000 & no left shift	2	3
Average	14,500	14,400

Many studies (17, 18) stress the role of concurrent medical problems in the elderly as the principal factor contributing to operative morbidity and mortality. Others, such as Hanswald (19), stress the role of the increased perforation

TABLE 6
Acute Appendicitis in the Elderly Population at The Mount Sinai Hospital 1974–84: Morbidity

	Controls 20–60 yrs (N = 56)	60+ yrs (N = 70)
Hospital stay*		
<10 days	77	26
11–20 days	18	46
>20 days	5	27
Average stay (days)	9.3	17.0
Complications**		
Wound infections	11	13
Total complications	18	37

* $p < 0.001$.
** $p < 0.025$.

TABLE 7
Postoperative Complications in Another Study

	50+ yrs (N = 100)	<50 yrs (N = 50)
Wound infections	14 (14%)	2 (4%)
Atelectasis or pneumonia	5	0
Abscess	8	0
Others	19	5
Total number of complications	46 (46%)	7 (14%)

Adapted from Hubbell et al, *S.G.O.* 3/60.

TABLE 8
Acute Appendicitis in the Elderly Population at The Mount Sinai Hospital 1974–84: Perforation Rate

	Controls 20–60 yrs (N = 56)	60+ yrs (N = 70)
Pathology*		
Nonperforated	66	32
Perforated	34	68
Perforated with abscess	16	30
Perforated with generalized peritonitis	5	7

* $p < .001$

TABLE 9
Acute Appendicitis in the Elderly Population at The Mount Sinai Hospital 1974–84: Delay in Diagnosis and Treatment

	Controls 20–60 yrs (N = 56)	60+ yrs (N = 70)
Time with symptoms before seeking care		
<12 hr	39	17
13–48 hr	43	40
>48 hr	18	43
Time from emergency room to operating room**		
<12 hr	80	58
13–72 hr	16	26
>72 hr	4	16

* $p < .005$
** $p < .025$

rate in the elderly, which is well documented. However, this perforation rate has been stated to be between 30% (10) and 71% (5), depending on the study. Clements (20) also stressed the effect of a perforation in the appendix on mortality rate. His series of patients from Otswego, New York, showed a mortality rate of 0.15% in nonperforated appendicitis, 4.0% in perforated appendicitis, and 9.5% in those with generalized peritonitis.

Summary

The high complication rate, mortality rate, and length of hospital stay in the elderly patients with acute appendicitis must be attributed, at least in part, to the high perforation rate in this group of patients. This study has documented the fact that elderly patients wait longer with symptoms before seeking medical care. This delay in hospitalization is the principle factor leading to the high perforation rate in the elderly. The etiology of this delay is less clear. Possible factors include lack of access to medical care and transportation, the disadvantage of living alone, confusing chronic gastrointestinal conditions, vagueness of symptoms, denial of serious illness, and the failure of family and friends to recognize the importance of abdominal pain in the elderly patient.

The elderly patient must be educated to the possibility of abdominal pain signifying serious illness that may require surgery (21). It is the physician's responsibility to educate both patients and their families and friends to seek medical care at the onset of surgical illness. In other surgical diseases, health education has been a major factor in reaching the disease process at an earlier stage. Acute appendicitis is no exception. With earlier clinical presentation, a significant impact on human suffering and financial cost to society could be made.

This study has also documented a statistically significant in-hospital delay in surgical treatment of elderly patients with appendicitis. This must also play a role in the high perforation rate. Possible causes of this delay include atypical clinical presentation, paucity of classical physical findings, failure of physicians to consider the diagnosis of appendicitis in elderly patients, reluctance to perform a negative laparotomy on elderly patients, overreliance on radiographic studies, increased incidence of other surgical conditions of the abdomen, and longer time required to evaluate and correct concurrent cardiopulmonary and other conditions.

The general medical community must be aware of the possibility of acute appendicitis in the elderly. If any doubt exists as to the possibility of appendicitis, surgical consultation should be obtained immediately. Laparoscopy may be a valuable tool in evaluating elderly patients with abdominal pain and preventing dangerous in-hospital delay (22).

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Catastrophic Vascular Emergencies in the Elderly

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Abstract

Rupture of aortic aneurysms and acute ischemia of the limbs are the most common vascular emergencies of the elderly. Mortality in ruptured aortic aneurysm is very high (50%–80%). In all good-risk patients, therefore, aneurysms should be resected electively. Symptomatic and expanding aneurysms and those larger than 6-cm in diameter should strongly be considered for elective surgery. Acute ischemia is usually due to embolization from the heart or acute arterial thrombosis. Diagnosis should be clinical, and surgery should be urgently considered.

The elderly are subject to two main groups of vascular catastrophies: rupture of aortic aneurysm and acute arterial occlusion of the limbs.

Aortic Aneurysms

An aneurysm is a dilatation of a portion of the arterial wall due to disease or injury. Aneurysms are classified as either true or false aneurysms. In a true aneurysm, the wall is the diseased artery. In a false aneurysm, the wall is not arterial in origin, but occurs in surrounding tissues. Etiologically, true aneurysms can occur secondary to congenital weakness of the wall (Marfan's syndrome, Ehlers-Danlos syndrome, Berry aneurysms) or to acquired problems (arteriosclerosis, syphilis, poststenotic, mycotic, arteritides). False aneurysms can occur secondary to injury to the arterial wall by gunshot, knife, or glass wounds or after arterial surgery (dehiscence of arteriotomy suture). In the elderly, the most common origin by far is the arteriosclerotic.

Arteriosclerotic aortic aneurysms can occur in any part of the aorta. The commonest location is in the abdominal segment, below the origin of the renal arteries. Most commonly, they are asymptomatic and are detected as an incidental finding during physical examination. A pulsatile mass is felt in epigastrium. Plain abdominal x ray can demonstrate a fusiform calcified image in front of the lumbar spine. An intravenous pyelogram will show lateral displacement of ureters. The diagnostic test of choice is the sonogram; it shows extremely accurately the size and location of the aneurysms. Arteriography is not useful diagnostically because the true lumen of the aneurysmatic portion is usually the same size as normal vessel. The extra lumen in the aneurysmatic cavity is filled with laminar clot. On some occasions, aneurysms can occur with such symptoms as gastroduodenal outlet obstruction, back pain (secondary to compression of retroperitoneal neurologic structures, erosion of the lumbar spine, or dissection in the aneurysmatic wall), embolization to the lower extremities, or erosion into the gastrointestinal tract with gastrointestinal bleeding. They occur most dramatically as ruptured aortic aneurysms. The majority of ruptures occur into the retroperitoneum. The patient complains of acute and severe back pain and has sudden hypotension. Many times, because of tamponade in the retroperitoneum, vital signs can return and remain for a while within normal limits. If nothing is done, the hematoma will continue to expand, and the patient will go into severe hypovolemic shock and die. Mortality in ruptured aortic aneurysms is 100% without

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surgery. The diagnosis, therefore, has to be rapidly established. Time-consuming diagnostic procedures should not be performed. The palpation of a pulsatile epigastric mass, associated with the findings already described, should be enough to make the diagnosis and proceed with emergency exploration. Surgical mortality in this situation is as high as 50%–80%.

The therapy for all aneurysms is surgical. Replacement of the diseased segment with a synthetic graft is the principle of therapy in the aortic location. In considering surgery, several variables have to be taken into account: (a) General condition of the patient. In good-risk patients, surgical mortality today is below 5% in most series. If there are risk factors such as congestive heart disease, chronic renal failure, or obesity, mortality can be as high as 50%. (b) Clinical presentation of the aneurysm. Symptoms such as gastrointestinal obstruction, bleeding, or back pain are ominous signs, usually preceding rupture. (c) Expansion proved with sonography is also a predictor of rupture. (d) Size of the aneurysm. It has been well documented that size is a very accurate predictor of rupture. The incidence of rupture increases dramatically above 6 cm in diameter. A 4-cm-diameter aneurysm has a 5-year risk of rupture of 15%. On the other hand, a 7-cm aneurysm has a 5-year risk of rupture of 40%. The risk increases as the diameter increases.

The final decision on surgical intervention will depend on the risk of the patient dying from untreated ruptured aortic aneurysm, versus the risk of surgical mortality for the particular patient. It is now well accepted that aneurysms of all sizes should be treated surgically in good-risk patients. In poor-risk patients, the decision will depend on the estimated surgical mortality and the particular characteristics of the aneurysm in question.

Acute Arterial Occlusion of the Limbs

A sudden block to arterial perfusion to the limbs can be due to local or general factors. Local factors include thrombosis of an artery, embolism, a prolonged tourniquet, spasms, cold injury, or a wrongly applied splint. General factors, such as poor blood flow in shock state, and blood dyscrasias, such as polycythemia, leukemia, thrombocytemia, and cold agglutinins, can also produce acute ischemia. The most common causes are acute arterial thrombosis and embolisms. Thrombosis occurs in a preexisting atherosclerotic diseased artery. In a very stenotic lumen, blood flow is severely restricted; eventually a clot is formed, producing complete arterial occlusion. In the embolic situation, a clot usually arising from the heart is lodged in a normal distal artery, producing a sudden block to arterial perfusion. Heart conditions, such as atrial fibrillation and previous myocardial infarction, are the most common causes of clots.

In acute ischemia, the nerves are the most sensitive to anoxia. The first symptom, therefore, will include pain, paresthesia, and paralysis. The extremity will be pale and cold, and no pulses will be palpable. More advanced ischemia will affect the muscle tissue. Muscle necrosis will be manifested by contraction of the muscle and increase in specific muscle enzymes. In advanced ischemia, the skin will become gangrenous.

Diagnosis of this entity is clinical. The acute onset of pain, paresthesia, and paralysis in a cold, pulseless extremity must be enough to make the diagnosis of acute ischemia. Immediate systemic heparinization should be considered at this point to prevent distal propagation of the clot and allow collateral circulation to be established.

The use of preoperative angiography will depend on the urgency of surgical intervention (If the limb looks severely threatened, no time should be wasted before exploration) and the general clinical presentation. If embolic phenomena are suspected, arteriography is not essential. In cases of thrombosis, bypass procedures will usually be required, and assessment of the distal arterial tree is important in planning the vascular reconstruction.

The surgical treatment of embolic arterial occlusion is embolectomy, using balloon catheters (Fogarty catheter). The use of long-term postoperative anticoagulation is essential in preventing new embolic events. Results using these techniques are very favorable. Limb salvage is in the range of 90%.

In cases of thrombotic occlusion, simple thrombectomy gives very poor results. The preexisting diseased artery will tend to reocclude again. In these cases, major vascular reconstruction may be necessary.

The Elderly Patient: Stress and Emergencies

Stress: Assessment and Intervention

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Stress and the Elderly Patient: Assessment and Intervention

Introduction

Physicians have long been aware of an association between stress and illness. The medical literature contains many clinical observations of emotional disorders or traumatic life experiences preceding the onset of significant physical illness. The multifactorial etiology of disease and the complex response of the organism to it have provided a background for extensive basic and clinical research into the apparent interplay between mind and body (1). It has been discovered that several adaptive responses in the neuroendocrine and immune systems play important mediating roles in that interplay, and experimental support has thus been provided for the premise that psychosocial factors can increase susceptibility to certain disease (2, 3).

Many of the so-called "hard data" indicating a strong causative relationship between stress and physical disease have rested on the results of animal experiments. Skinner (4), for example, showed that relocating a pig in a new environment and surrounding it with unfamiliar objects raises the animal's serum level of myocardial phosphorylase and increases the vulnerability of the myocardium to ventricular fibrillation and sudden death. He furthermore demonstrated a pathway from the frontal cortex to the hypothalamus to the brainstem, stimulation of which by psychological stress resulted in myocardial necrosis and ventricular fibrillation similar to that produced by large doses of catecholamines (5). Sapolsky, Krey, and McKewen (3) have shown that, in the aged male rat, there is an impairment of the mechanism whereby the secretion of glucocorticoids is terminated at the end of stress. The impairment may be caused by age-related degeneration of hippocampal corticosterone receptors which normally mediate the inhibition of glucocorticoid release.

Preliminary evidence suggests that the leap of faith required to accept the findings of such experiments as appropriate models for human disease may not be great. The statistical evidence of increased death rates in elderly human subjects following bereavement and relocation is very convincing (6, 7).

Sussman, in his paper "Stress and Medical Illness in Later Life," attempts to delineate the impact of specific social and environmental events on the health status of the elderly. Among the more commonly investigated stressors he notes are social isolation, bereavement, retirement, and relocation. He reports that investigations have shown that social support, in the form of close relationships, may buffer the impact of stress on the health of older adults. Conversely, social isolation may be a risk factor for both morbidity and mortality, and he provides several studies in support of this fact. The stress of conjugal bereavement is such that the mortality rates of people who have recently lost their spouses is 1.4 times higher than those still married (8).

Relocation is another stressor among the elderly, especially from home to an old-age home. Rowland (9) has documented these findings. Retirement may be a stressor to some individuals, particularly to those who are reluctant to retire, as shown by Ekerdt and associates (9). Sussman recognizes an emerging body of evidence suggesting a causal relationship between life events and physical illness and a particular suscepti-

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The papers in this section are all based on presentations at Kingsbrook Jewish Medical Center, Brooklyn, NY, on Oct. 15, 1985, at the eighth annual Geriatrics Seminar.

bility of the elderly to stress, whatever the contrary data. He is impressed by the work of Sapolsky and associates (3), which appears to be a model for humans, and the evidence of increased death rates following bereavement and relocation is important.

As noted by the authors of this symposium, the effect of stress on many discrete systems (including the cardiovascular, pulmonary, gastrointestinal, endocrine, and immune systems) has been extensively studied in humans.

Cardiovascular. Meyer Friedman, one of the earliest investigators of the Type A personality, which is characterized by aggressive, hostile, and competitive behavior, long ago observed a direct correlation of this personality type with increased risk of myocardial infarction (10). In his paper "Modifying Type A Behavior of Patients after Myocardial Infarction: Effect on the Recurrence Rate," Friedman now offers further evidence that victims of myocardial infarction who subsequently receive not only conventional cardiologic counseling, but also group counseling designed to modify Type A behavior patterns, may be expected to benefit from a significant reduction in the recurrence rate when compared to patients who receive only conventional counseling or no counseling at all. Elsewhere, Engel (11) has emphasized the important role played by feelings of helplessness, hopelessness, and profound disappointment as precursors of myocardial and other physical disorders. Park and associates (12) reported a significant increase in the incidence of acute myocardial infarction in recently bereaved widows. Their data suggest that a significant proportion of deaths have been advanced by the stress of loss.

In the paper in this issue by Kennedy and Fisher, "Aging, Stress, and Sudden Death," age-related stresses (bereavement, social isolation, retirement, dissatisfaction, changes in life events and household size) have been empirically linked to cardiovascular mortality, and there is reason to believe that the unifying emotional result of these stresses is episodic depression. In a prospective study of 88 patients treated acutely for life-threatening arrhythmia, follow-up mortality was found by the authors to be significantly related to depression and cognitive impairment found at initial assessment. Kennedy and Fisher suggest that psychosocial intervention for patients at risk for sudden death should focus on reduction of age-related stressors through aggressive treatment of depression and early identification of and preparation for the behavioral sequelae of cognitive impairment. They further propose that, as therapeutic advances increase the number of arrhythmia survivors, the prevalence of dementia of vascular etiology may proportionately increase and that some degree of the observed morbidity and mortality may be attributed to depression and dementia. The possibility of a correlation between certain forms of mental illness and malignant cardiac arrythmias is made enticing by the accumulation of evidence that links neural activity with the development of ventricular fibrillation. Lown and his co-workers (13) have demonstrated that hypothalamic stimulation provokes ventricular fibrillation in animals with or without coronary artery occlusive lesions.

The study by Ruberman and co-workers (14) provides additional data to substantiate the notion of a causal role for biobehavioral stress in cardiac death. They observed that high indices of life stress and social isolation, independent of other variables, were significantly associated with a high risk of cardiac death. Graboys (15) recognizes that these considerations underscore the need for physicians to elicit a social history from their patients with ischemic heart disease before we proceed to technologic forms of diagnostic evaluation.

Pulmonary. Effects of stress on the pulmonary system have also been studied. Asthma in the elderly is not uncommon. Random surveys have shown that, based on symptoms, a physician would consider the diagnosis of asthma in up to about 13% of elderly people (16). Knapp and Mathe (17) have suggested that emotional factors may indeed play an important part in initiating and sustaining the clinical changes in bronchial asthma. Acute changes in airway conductance occur in response to psychosocial stimuli in certain subjects. Presumably these are mediated primarily by the parasympathetic nervous system, that is, by vagal influences on the upper airways (17). In the matter of therapy, it is worth emphasizing that asthmatics, whatever their age, frequently become anxious about the state of their health, and the good physician will treat this anxiety by effective management of the asthma and by reassurance. The poor physician will give sedatives and tranquilizers. Crocco, discussing "Stress and the Lung: Hypersensitivity of Airways, Neurogenic Pulmonary Edema, and Hyperventilation Syndrome" in this symposium, indicates that these disorders are common in the elderly and that stress in this population may be a significant contributor to acute exacerbation and refractoriness to management. Crocco emphasizes that physicians managing hyperventilation syndrome and neurogenic pulmonary edema must increase their awareness of the psychobiological factors that influence the respiratory systems of both young and elderly, and that only combined observation of the physiological, psychological, and environmental factors allow the physician to see the whole problem and thereby institute proper and complete therapy. It is the view of Crocco that the three conditions discussed represent only a small fraction of the pulmonary conditions in which stress is an operant.

Gastrointestinal. Berman, in his paper "Stress and the G.I. Tract," acknowledges the problem that many of the data correlating gastrointestinal disease with stress depend heavily on inference to sustain a causal relationship. The difficulty is compounded by the subjective nature of the manifestations of stress and by its seemingly pervasive character. Attempts to link stress to esophageal disease, the peptic ulcer diathesis, irritable bowel syndrome, and inflammatory bowel disease all suffer under this dilemma. Berman, however, finds in the stress ulcer syndrome an important key to unlocking the mechanisms by which stress produces disease. Conflicting experimental results abound, but the final common pathway to account for the ulcer diathesis may be a failure of the gastric mucosa to cope with the lumenal acid with which it is presented. The precise role played in this cytoprotective breakdown by diminished gastric mucosal blood flow and decreased prostaglandin synthesis, and the manner in which these parameters are manipulated by stress, are still unclear and remain to be elucidated. Berman concludes that, despite the inconclusive evidence, clinicians appropriately pay considerable attention to stress in their management of gastrointestinal disorders.

Visual Function. Wolintz and Miller have evaluated the relevance of stress to disorders of visual function and conclude that it may indeed contribute to various forms of ophthalmologic disease. They discuss the relationship between stress and essential blepharospasm, thyroid ophthalmopathy, uveitis, glaucoma, and multiple sclerosis. In the first two of these conditions the authors propose a primary role for stress, and in the other conditions a possible intermediate role. Many authorities, we are told, believe that emotional stress is a precipitating factor in the recurrence of some forms of uveitis.

In the same paper, the authors discuss the problem of relieving the stress associated with blindness as well as the services and devices available to the blind to assist them in coping with the condition and improving the quality of their lives.

Immune System. The existence of a hormonally mediated link between psychosocial stressors and impaired immune function is supported by several observations. Lymphocyte metabolism and proliferation are inhibited by increased production of corticosteroids. Lymphoid organs atrophy as a result of chronic stress. Natural killer-cell activity is adversely affected by corticosteroids and catecholamines (18).

The autonomic nervous system, unquestionably responsive to stress, has, in common with the action of corticosteroids, an inhibiting effect on cell-mediated immunity. Decreased numbers of lymphocytes are found following prolonged psychosocial stress. Other circulating cells, such as mast cells, neutrophils, and macrophages, are also affected to varying degrees.

Studies of sleep-deprived human subjects have revealed elevations of stress-related hormones; moreover, although the ability of lymphocytes to produce interferon appeared to increase, the ability of neutrophils to phagocytize *Staphylococcus aureus* diminished (20).

Abnormalities of immune function have been found in bereaved humans and in those suffering from major affective disorders. Observations of increased morbidity and mortality in individuals following the death of a spouse have been made since records began. The "attributable risk of mortality" has been reputed to be as high as 50% in conjugal bereavement and is, predictably, especially high for men in the older age groups (6). In a prospective study of 15 spouses of women with terminal breast carcinoma, Schleifer et al (21), testing the mitogenic response of lymphocytes to stimulation by phytohemagglutinins, concanavalin A, and pokeweed mitogen, found a significant depression of the response in the first two months following bereavement, with intermediate responses in the follow-up period. The changes could not be accounted for by changes in nutrition, levels of sleep activity, or abuse of any substance.

Schindler (1), in a discussion of stress, affective disorders, and immune function, cites increasing scientific evidence supporting the age-old popular wisdom that psychosocial factors are associated with pathogenesis of many physical and mental illnesses. The immune system appears to play a primary mediating role and prolonged or poorly controlled stress may depress various components of immune function. In her view, these responses may be related to or independent of changes in the neuroendocrine system.

In her article Schindler reflects that recognition of the multiplicity and complexity of the factors that interact to produce disease must result in an alteration of the physician's approach to disease itself and, thus, also to his patients as they are evaluated and treated in the psychosocial context of their lives. I join her in this prediction and this hope. Moreover, it is my strong belief that the data provided by the authors presented here indicate that we are no longer operating in a scientific twilight in relating stress to human illness.

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Stress and Medical Illness in the Elderly

NORMAN SUSSMAN, M.D.

Old age is often perceived as a period of increased psychosocial stress and of diminished capacity to cope with the multiple life changes the elderly experience (1–4). Retirement, physiological decline of their bodies, death of loved ones, social isolation, and relocation to a nursing home are some of the major stresses the elderly face. While many physicians and social scientists believe stress adversely affects the health of the elderly, others argue that this relationship has not been conclusively established. This review attempts to discuss representative research and opinion on basic issues in the concept of stress as a pathogen and the significance of stressful events in the elderly.

Underlying Mechanisms

In demonstrating the relationship between stress and illness, it is important to identify anatomic and physiologic pathways that underlie postulated stress-related pathology. Early research focused on cardiovascular and endocrine systems; more recent investigations have examined the immune system.

Cardiac Disturbances. Numerous studies have shown that psychosocial factors can produce potentially damaging or lethal disturbances in myocardial function (5–7). Sudden death syndrome is frequently attributed to stress. These deaths, which occur within minutes of symptom onset, are hypothesized to be related to ventricular fibrillation and acute myocardial ischemia. Infarction and thrombosis are not typically involved. Lown and his associates characterize the syndrome as an "electrical accident" (8). In nearly half of cardiac patients they studied, psychologic stress was shown to increase the number of ventricular ectopic beats. Their work suggests that psychologic stress mediated through higher nervous system activity can precipitate the sudden death syndrome.

Other studies support these findings. Both Natelson (9) and Talman (10) have reviewed the literature on the role of the nervous system in cardiovascular regulation. Citing numerous studies, Talman describes how emotional stress can alter sympathetic activity and precipitate cardiac arrhythmias. Deanfield and associates (11) used positron tomography to assess the effect of mental stress (solving math problems) and physical stress on the flow of blood to the heart. They observed an obvious association between mental activity and myocardial ischemia: 75% of the patients experienced abnormalities of regional myocardial perfusion. Moreover, these disturbances occurred at significantly lower heart rates than those that accompany physical exercise.

Endocrine and Immune Function. Endocrine function was one of the earliest subjects of stress research. In the 1930s, Hans Selye hypothesized that the stress response was mediated by the adrenal glands (12). He developed the concept of a "general adaptation syndrome," which produced a nonspecific response of the body to both physical and psychosocial stressors. Selye described three stages: an alarm reaction, resistance, and exhaustion, depending on the severity and duration of the stressor. His experiments with animals demonstrated that extreme stress increased hormonal secretion from the pituitary and adrenal glands.

Experiments on aged rats indicate they are less able to regulate the sympathetic-adrenal medullary during and after exposure to stress (13). These data are consistent with the general view of a progressive decline in regulation of en-

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docrine and renal functions with age. This cascade of physiologic alterations could underlie the diminished capacity of the elderly to cope with a stressful environment.

Jacobs and his coworkers (14) have studied 24-hour urinary epinephrine and norepinephrine in middle-aged and elderly persons who were either acutely bereaved or threatened with the loss of a spouse. The researchers found that the output of both catecholamines during acute bereavement is elevated above normal, but not to a degree associated with adrenal medullary disease. No differences were observed between those who had recently experienced an actual loss and those who were threatened by a loss. An association was found between increasing age and higher levels of urinary catecholamines among acutely bereaved subjects. The researchers postulate that this finding reflects slower adaptation of the sympathetic-adrenal medullary system to stress among the elderly. They conclude, "It is possible that the chronic stress of bereavement for elderly bereaved persons leads to sustained sympathetic-adrenal medullary function at a high level and particularly slow adaptation by comparison with younger, bereaved counterparts."

A compelling body of research on the endocrinology of stress and aging has come from Sapolsky, Krey, and McEwen (1). They have studied a number of themes in gerontology concerning "the capacity of aged organisms to respond appropriately to stress to cumulatively damage aging tissue." Specific questions that they have addressed include whether advanced age is characterized by decreased adaptiveness to stress and whether chronic stress accelerates the aging process. The researchers have convincingly demonstrated in aged male rats a normal capacity in initiating the stress response but impairment in terminating the secretion of adrenocortical stress hormones, glucocorticoids, at the end of stressful events. The resulting hormonal excess is postulated to be due to the loss of hippocampal corticosterone receptors. These degenerative changes in a region of the brain which normally inhibits glucocorticoid release is actually caused by cumulative exposure to glucocorticoids. In other words, hypersecretion of glucocorticoids (elevated basal glucocorticoid concentrations) result in insensitivity to glucocorticoid negative feedback. This "feed-forward cascade" can be used to explain a variety of age-related pathologies.

More recently, other postulated descriptions of potential pathways of stress-promoted neoplasia involve increased corticosteroid levels with subsequent decrease in T-cell growth factor (15). Stress-prone individuals may also experience elevated epinephrine levels and stimulation of c-AMP, which may cause immunosuppression. Baker and associates (16) hypothesized that stress and other emotional factors may be important factors in both susceptibility to disease and disease outcome.

Locke and associates (17) studied a group of healthy undergraduate volunteers to test whether stress was associated with alterations in cell-mediated immunity. They correlated self-reported life-change stress and psychiatric symptoms with natural-killer cell activity. Subjects with few psychologic symptoms despite severe life-change stress (good copers) had significantly higher natural-killer cell activity than those experiencing more stress-related psychiatric symptoms. Schleifer and associates (18) found decreased lymphocyte (T-cell) function in depressed patients and suggested that altered immunity may be related to severity of depressive symptoms.

Definition and Measurement of Stress

Central to all studies of the relationship between life experiences and physical health is the need to define what constitutes stress and then how to measure it. A half century has passed since Selye made stress a topic of serious scientific study, but a definition of the term remains elusive. As Marmot (19) observed, what is stressful to one person may be stimulating to another and may, in fact, produce positive change. Even if arbitrary definitions are provided, it is still difficult to grade or quantify the stressfulness of life events.

The best known of the attempts to define and measure stress is the work of Holmes and Rahe (20), published in 1967. They defined a stressor as an event which causes change in one's usual way of life. They postulated such social change requires adaptation and leads to an alteration in various physiologic systems, which in turn increases the risk of becoming ill. This concept of stress also included experiences that are generally regarded as positive or pleasant. For example, a vacation, job promotion, or marriage might require as much social readjustment as events considered to be a hardship.

Holmes and Rahe developed a social readjustment scale—a table of 43 life events perceived by subjects of their research to require significant psychosocial adjustment. They found a positive correlation between the number and severity of the life events and increased risk of illness. The stressors ranked highest on this scale are also those most common in old age. They include death of a spouse or close family member, personal injury or illness, retirement, change in health of family member, sex difficulties, change in financial status, and death of a close friend.

Many investigators, however, have not found this scale to be useful in predicting risk of disease (21). Weinberger and his associates (22) found that the elderly reported better health if they experienced more events perceived as positive and fewer viewed as negative during the preceding year. He also found the elderly more sensitive to adverse change, regardless of the degree of adjustment involved. Other studies challenge the inclusion of certain life events as stressors. For example, the "empty-nest syndrome" has been cited as a stressor. Palmore and associates (2) reported that many parents viewed the event of the last child leaving home as having a positive rather than negative effect on their lives.

Stressful Events of Later Life

Attempts have been made to delineate the impact of specific social and environmental events on the health status of elderly adults. Among the more commonly investigated stressors are social isolation, bereavement, retirement, and relocation.

Social Isolation. Investigations have shown that social support, in the form of close relationships or informal networks, may buffer the impact of stress on the health of older adults. Conversely, social isolation may be a risk factor for both morbidity and mortality. In a study of 2,320 males who had experienced a myocardial infarction, those with high levels of stress and social isolation had four times the risk of death in a three-year period than men with low levels of both stress and isolation (23). Cohen and associates (24) studied 133 elderly residents of inner city hotels and reported that social networks reduced physical symptoms perceived by these residents.

Berkman and Seeman (4) have reviewed the published literature on the relationship of social networks or social isolation to mortality risk. "Of the seven mortality studies published to date," they observe, "social isolation and lack of support is consistently associated with an increased mortality risk among white men . . . they convince us that something about human relationships influences physical health and especially longevity." It is unexplained why the findings regarding white men are so striking.

Conjugal Bereavement. Several studies comparing morbidity rates of people who have recently lost their spouses to those who are married found in all age groups that the widowed have death rates 1.4 times higher than those still married (25). Three prospective studies found increased mortality rates during the first 6 to 12 months following the loss of a significant other, compared to controls (26–28). Parkes (29) reports a statistical association between bereavement and death from heart disease, and Clayton (30) found men, especially older men, had a higher risk of death in the first six months of bereavement.

A prospective study of widowers during the first two months following the death of a spouse found significantly decreased lymphocyte response compared to prebereavement levels (31). This finding suggests that a suppressed immune state following bereavement may be responsible for some increased mortality.

McAvoy (32) has summarized the various mechanisms that have been suggested to explain higher mortality after bereavement. Impaired immune function is addressed in the "desolation effects hypothesis", which posits that grieving and adjustment not only directly impair resistance to disease, but also indirectly increase vulnerability to illness through unhealthy behavior such as increased use of alcohol or tobacco or both. Similarly, the "loss-of-care hypothesis" holds that the surviving spouse neglects basic social, medical, nutritional, and hygiene needs simply because of being alone.

Relocation. The emotional stress associated with relocation, especially from home to an old-age home, is familiar to those who work with patients. Increased morbidity and mortality rates associated with residential moves of the elderly have been documented (33).

The loss of familiar surroundings and disruption of social networks are major sources of distress. Recent loss of a wife in conjunction with moving into an old-age home has been reported to significantly increase mortality rates (34). This study also showed that the mortality rate of those who remarried fell to expected levels. Booker (35) reported severe electrolyte disturbances in elderly patients who had been stabilized on diuretics as outpatients after admission to a nursing facility.

But the causal relationship between the

stress of relocation and increased morbidity and mortality in the elderly remains unclear. Many elderly patients are relocated because of their deteriorating health status.

Retirement. Although it has been commonly assumed that retirement may cause a decline in physical and mental health, a number of studies have found that health may improve upon retirement. A longitudinal study carried out on a randomized sample of male managers found that retirement might reduce the age-related increase in morbidity (36). When subjects were examined after three years, the rate of heart and artery disease was significantly greater in nonretirees than in retirees. In a retrospective study, Ekerdt found health may improve after retirement (37). It has been noted, however, that some individuals who are reluctant to retire may suffer health effects if forced to retire (38).

Mediating Factors

Certain factors are presumed to predispose to or to protect against stress-related pathology. Most commonly these moderators of the stress response are described in terms of personality and behavior.

The most notable attempt to delineate a specific "illness-prone" personality is the work of Rosenmann and Friedman (39) on behavioral patterns and predisposition to coronary artery disease. They reported that individuals with Type A behavior (characterized by easily aroused anger and hostility, impatience, competitiveness, hard-driving and time-pressured job involvement, and vigorous voice and psychomotor mannerisms) had twice the risk of developing coronary artery disease than low-key Type Bs. Recent work by other researchers indicates that Type A individuals who typically suppress their anger rather than express it may be at a greater risk for coronary artery disease (40).

Two mechanisms have been postulated to account for this association of Type A behavior with coronary risk. One is increased levels of cardiovascular activation (hyperresponsiveness), as measured by increased blood pressure and noradrenalin output, to challenging situations. But the other, the process leading to atherosclerosis and obstructed coronary arteries, remains unknown.

Scher and associates (41) monitored phasic changes in heart rate and ECG T-wave amplitude in healthy individuals during periods of stressful mental activity. Type A subjects showed greater T-wave amplitude than Type Bs. Such ECG responses sometimes precede the appearance of clinically significant coronary pathology.

However, two studies of patient outcome following myocardial infarction failed to find a statistically significant influence of Type A behavior pattern on mortality rates (23, 42). These studies leave the concept of a coronary-prone behavior complex open to question. The relevance of Type A construct to old age has not been determined.

As discussed above, social support may be one of the most important mediators of the stress response in the elderly. Coping behavior may also play an important role. Dessonville (43) suggests that older persons may consciously or unconsciously anticipate and prepare for adverse events well in advance. Illness, physical decline, widowhood, retirement, and other postulated stressors of late life may represent "on-time" events. Dersonville reports that elderly patients who have the most difficulty adjusting to such events are those who cannot come to terms with role changes, losses, and decline in physical capacity.

The possibility that the elderly may be immune to certain situations or life events identified as stressful in younger persons was investigated by Halpert and Zimmerman (44). They reported a relative sense of well-being among "old-old" patients (those 75 years and older) compared to those age 60 to 74. The older group reported less depression, anxiety, and nervousness and appeared to be in better control of their lives, despite reduced income and increased health problems.

Conclusions

The elderly are the fastest growing section of the population, and they experience high rates of morbidity and mortality. For those who plan and provide health care to the elderly, it is important to identify specific circumstances or events that are associated with adverse stress reactions and provide appropriate interventions. As this review has attempted to show, there is an emerging body of evidence that suggests a causal relationship between life events and physical illness and a possible particular susceptibility to stress in the elderly. Not all researchers agree that the evidence is sufficient to prove stress is an important factor in disease onset and outcome. As Angell pointed out, "The known physiologic effects of stress on the adrenal glands are often over-interpreted so that it is a short leap to a view of stress as a cause of one disease or another . . . it is not enough to point to the plausibility of a chain of events leading from emotional stress to increased adrenal activity to immune suppression to cancer" (45). Nevertheless, the work of Sapolsky and his associates (1) does seem an appropriate model for humans, and the evidence of increased death rates following bereavement and relocation is convincing.

In reviewing the literature on stress, illness, and old age, a number of methodological limitations and potential sources of error in forming conclusions are evident. The latter include selective citation of studies, failure to distinguish between physical and psychosocial stressors, overinterpretation of the meaning of the study's findings, generalizing findings in a homogeneous adult population to elderly adults, and failure to document preexisting health status. If study groups are not carefully matched in terms of preexisting health status, it is impossible to distinguish which physical manifestations are secondary to stress and which to natural progression of disease. Whether a person is at risk of the adverse effects of stress may be more dependent on underlying health than on age.

There is also the possibility that the very elderly are less, rather than more, susceptible to stress following certain life events—the "survivorship phenomenon." Older adults may be seen as a select group who, by virtue of reaching advanced age, have demonstrated superior adaptive abilities.

It is clear that at the very least psychosocial factors can produce distress and reduce satisfaction, resulting in diminished quality of life. It is also likely that life events are the triggers of death or disease in the complex group of elderly patients who may already by debilitated by or have significant undetected illness.

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Effect of Modifying Type A Behavior after Myocardial Infarction on Recurrence Rate

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Abstract

In a study now called the Recurrent Coronary Prevention Project, 1,012 postmyocardial infarction patients were randomized and enrolled in two sections; one section (270 patients) received cardiologic counseling and the other (592 patients) received both cardiologic and Type A behavior counseling. The remaining 150 patients served as a "comparison" group and received no group counseling of any kind. At the end of three years, 79% of those subjects who continued to receive Type A counseling demonstrated a reduction in the intensity of their Type A behavior. Individuals given cardiologic and Type A behavioral group counseling during the first three years of the study had an infarction recurrence rate of 2.7%. This was one-half the recurrence rate observed among participants given only cardiologic group counseling (5.4%), or no group counseling at all (5.2%).

After reviewing a large number of epidemiologic (1–5), clinical (6–10), and pathologic studies (11–14) of coronary heart disease, a panel of prominent investigators convened at the request of the National Heart, Lung and Blood Institute (NHLBI) focused on the possible relationship to the disease of Type A behavior—a deep-seated emotional disorder whose overt characteristics are a sense of time urgency and easily aroused hostility (1, 14). They declared (15) that this type of behavior was a coronary risk factor and that its pathogenic potential was as great as any of the commonly accepted coronary risk factors: hypertension, hypercholesterolemia, and cigarette smoking.

Although gratified by the panel's conclusion that Type A behavior is a coronary risk factor, we strongly suspected that commonly accepted coronary risk factors (hypertension, hypercholesterolemia, excessive cigarette smoking, and some cases of maturity-onset diabetes), far from being independent of Type A behavior, may be initiated or worsened by it. In effect, we believe that most coronary risk factors are sequelae of Type A behavior. The risk factors appear to be mediated by the damage done to the coronary arteries.

Some research cardiologists and the majority of epidemiologists previously reluctant to accept the concept that a person's feelings may have as great or greater deleterious effect upon coronary vasculature than what he or she ingests are coming around to this viewpoint. However, others confronted with this 1981 report declared that Type A behavior is a personality disorder that cannot be changed and hence should remain neglected, as it had been for the more than two decades since the first announcement of its intimate association with coronary heart disease (CHD) (1).

From personal experience with a number of patients with CHD treated privately in the 1960s, I was convinced that the intensity of Type A behavior could be significantly lessened in most. Moreover, in most cases, it was more easily accomplished than altering diets and cigarette smoking habits.

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Based on my preliminary clinical experiences, I attempted to alter the Type A behavior pattern in a large enough number of my patients so that the results might be statistically significant. In that way, these results would not be summarily dismissed as "anecdotal."

Finally, after assembling a research team of cardiologists, psychiatrists, psychologists, and paramedical personnel, plus funding from the NHLBI, I began a study which is now called the Recurrent Coronary Prevention Project (RCPP). In essence, 1,012 postinfarction subjects, men and women, were enrolled to determine two things: (a) whether the intensity of Type A behavior could be significantly reduced; (b) if reduced, whether such reduction would lead to increased protection against recurrent myocardial infarction.

Methods

Subjects. Briefly summarized: participants in the RCPP were under 65 years of age; were not diabetic; were nonsmokers, or had quit six months earlier; and had suffered one or more myocardial infarctions six or more months prior to enrollment (16).

Of 1,012 enrolled subjects, 862 were randomized into three sections. In Section 1 were 270 subjects receiving cardiologic counseling consisting of advice from their own physicians, diet, and exercise habits, and encouragement to adhere to their regimen. Subjects in Section 2 received the same cardiologic counseling, plus Type A behavioral counseling. Section 3 consisted of 150 individuals not enrolled in the other two groups who were willing to be examined yearly as a "comparison" or control group.

We envisioned that follow-up study of these 150 subjects, whose entry characteristics were essentially the same as all other participants', would serve two purposes. First, the prevalence of Type A behavior observed in these patients would reflect more accurately the prevalence of Type A behavior in all postinfarction patients than the observed prevalence rate in our two randomized groups. Second, this control group would never meet for any type of group counseling; hence recurrence rates observed in its members might serve as the standard.

If nonspecific group counseling, regardless of context, does affect cardiac recurrence rate, the recurrence rate in Section 1 subjects should be less than that observed in the control group. If such a difference were found, any reduction in cardiac recurrence rate in Section 2 patients receiving Type A behavior counseling could not be ascribed solely to the counseling they received, and the possible effects of nonspecific psychological group counseling on cardiac recurrence rate would have to be taken into account.

Any Section 1 or 2 participant who missed three successive meetings without giving an acceptable excuse was designated a "treatment failure." In addition, any Section 2 participant who refused to practice the drills assigned to all Section 2 participants was designated a "treatment failure." All such "treatment failures" (classed as Section 4) continued to be reexamined yearly.

At entry, the typical participant in all three sections was 53 years old, 69 inches tall, weighed 170–179 pounds, was married, and had graduated from high school. Enrollees included 84 women, 18 blacks, and 3 Asians.

Examinations. On entry, all patients (16) received a cardiovascular examination, including a resting electrocardiogram, serum cholesterol level, and urinalysis. This was repeated every 18 months. In addition, past hospital records of all patients were reviewed to calculate the Peel index (17) (chiefly on the basis of the occurrence of shock, complex arrhythmias, congestive heart failure, cardiomegaly, and appearance of new Q waves during the last infarction), which has been found to provide accurate prognostic guidance on possible recurrent cardiac events in postinfarction patients.

A "cardiac recurrence" was defined as either a new myocardial infarction (documented by appearance of new Q waves in the electrocardiogram or increase in blood level of diagnostic cardiac enzymes) or sudden cardiac death.

Modes of Measuring Type A Behavior. Previous attempts to diagnose the presence of Type A behavior have been seriously flawed by employing a stereotyped questionnaire or a so-called structured interview by scantily trained nonmedical personnel. Almost all the chaos and confusion surrounding the role of Type A behavior in the pathogenesis of CHD has stemmed from studies of subjects in whom presence or absence of Type A behavior was determined by responses to oral or printed stereotyped questions.

In this study, each participant at entry filled out a specially designed self-report questionnaire (the Participant Questionnaire). The actual diagnosis, however, of Type A behavior and estimation of its intensity were accomplished by a videotaped clinical interview (VCI). This method of diagnosis, described previously in considerable detail (16, 18, 19), consists of observing diagnostic nonverbal signs and eliciting the specific symptoms of Type A behavior. Repeatedly, the use of the VCI in this study led to the detection of Type A behavior in participants whose behavior was registered as Type B in either the Jenkins Activity Survey (3) or its Framingham derivative (5). In addition, Section 2 participants were asked to have specially designed questionnaires filled out by their spouses (the Spouse Questionnaire) and a colleague at work (the Monitor Questionnaire), to counterbalance possible bias in the participants' own questionnaires. Section 1 and 3 participants were not asked for either of these special questionnaires, to avoid increasing their awareness and possible self-correction of Type A behavior.

All questionnaires were obtained at entry and then yearly. The VCI was administered to all participants at entry and again at the end of three years by the same interviewer, who was never informed of the section status of any subject.

Counseling Program. The 22 groups of Section 1 participants (approximately 10–12 participants per group) received bimonthly nonspecific cardiologic counseling. The 60 groups of Section 2 participants received, monthly, the same nonspecific cardiologic counseling, plus Type A behavior counseling by a psychologist, psychiatrist, or cardiologist experienced in this type of counseling.

The Type A counseling program, while it incorporated initial instruction in progressive muscle relaxation, consisted chiefly of these procedures:

1. Recognition of the basic covert components responsible for and sustaining the overt manifestations of Type A behavior: sense of time urgency and easily aroused or free-floating hostility.

These basic covert components appear to be a combination of inadequate self-esteem and insecurity—phenomena usually, but not invariably, having their provenance in the early unsatisfactory parental relationships experienced by approximately 70% of our subjects.

2. Correct attribution of the factors responsible for personal achievements as well as failures.

Unfortunately, despite the fact that initiative, good judgment, hard work, creative thinking, charm, loyalty, and integrity had been responsible for whatever successes had been achieved by our Type A postinfarction patients, they were almost obsessively inclined to ascribe their successes to the sense of time urgency and free-floating hostility making up their Type A behavior. Rarely were they aware that it was precisely these two overt manifestations of Type A behavior that were often directly responsible for whatever serious mistakes they had made, including the very serious one of accelerating the onset of crippling myocardial infarction.

Throughout the entire counseling period of three years, we found it of paramount importance to repeat the process of linking Type A behavior with past as well as present failures, rather than successes. It is probably the underlying insecurity of these individuals which so persistently impels them to treasure their sense of time urgency and to rationalize their free-floating hostility.

3. Identifying and recognizing the psychomotor and biographical manifestations of Type A behavior.

Early in our counseling program, all Section 2 participants were taught the overt or psychomotor manifestations (the characteristic facial, vocal, body, hand, and leg signs) as well as the biographical aspects of Type A behavior (their past tendencies to hurry, to "over-drive," and to react angrily to venial errors of commission and omission by others). Audio-video tapes were frequently employed in illustrating Type A behavior. The purpose of this instruction was to enable the participants to discern their own signs or symptoms heralding the onset of Type A behavior so that they could take countermeasures.

4. Instruction in the probable pathophysiologic pathways by which Type A behavior leads to recurrences of myocardial infarction.

Excess norepinephrine secreted by the Type A person, whether healthy or a coronary patient, was first observed by us (6–9) and subsequently confirmed by others (18, 19). Excess ACTH is also secreted by Type A persons (10). The role of both secretions in the pathogeneses of clinical CHD now is suggested by a number of clinical and experimental observations.

Exactly how an excess of either hormone leads to recurrent myocardial infarction or sudden cardiac death remains to be determined. However, we strongly suspect that an excess of circulating norepinephrine (and possibly ACTH) may lead to the chronic constriction of adventitial arterioles supplying the coronary arteries, which may accelerate the decay so often taking place in old coronary artery plaques. As we demonstrated earlier (20), such areas of decay degenerate into "abscesses" which, if near the luminal surface of a plaque, rupture and, in so doing, produce the thrombotic occlusion initiating an infarction.

In short, we believe that the cardiac catastrophes so frequently occurring in postinfarction subjects are due either to the norepinephrine-accelerated decay and rupture of one of the old coronary plaques leading to infarction, or to a norepinephrine-induced ventricular fibrillation.

These laboratory and clinical observations and our beliefs relating them to recurrent myocardial infarction formed the basis of a lecture delivered to all Section 2 subjects early in counseling. Moreover, the chief pathophysiologic facts of this lecture were repeatedly reiterated throughout the three years of prophylactic therapy. We believe that postinfarction patients should be fully and repeatedly informed about the pathophysiologic realities of their condition. To these pragmatic persons, we offered a down-to-earth, no-holds-barred summary of their situation and its sinister potential. I am not at all sure that our program would have secured the results it did if this component of the counseling program had been omitted or trivialized. A fully informed postcoronary patient is far more receptive and cooperative.

5. Realistic evaluation of personal qualities.

One of the basic covert components, and perhaps the "driving engine," in the development of Type A behavior is inadequate self-esteem. William James, in his classic monograph "The Principles of Psychology" (21), points out that the self-esteem of an individual varies according to the equation: achievements/pretensions. Substitute "expectations" for "pretensions" in this equation and one understands Type A behavior and its fundamental differentiation from Type B behavior. Type A behavior, with extraordinarily few exceptions, arises when expectations far exceed achievements. It is unreasonable, unlimited expectations—whatever the person's accomplishments—which fuel the fires of the Type A syndrome.

In strong contrast, the Type B person possesses adequate self-esteem, not necessarily because of greater achievements than the Type A subject, but rather because of reasonable expectations that are not excessive. Reasonable expectations, I believe, initially arise out of early love and affection from both parents. Such a person does not feel in youth the need to overcompensate for any failure to obtain this tremendously powerful emotional and spirit-enhancing accouterment for one's journey through life. Its possession confers equanimity upon the Type B person; its absence confers emotional inadequacy upon the Type A person.

To modify this emotional inadequacy and the ceaseless striving it induces in our Type A patients, we strove to get them to catalogue all their personal qualities (good and bad, productive and destructive) and to assay them realistically, a process the Type A person almost obsessively shies away from. Typical Type A people prefer to delude themselves with the unreal belief that their qualities are beyond reproach and that all that is required to reach their achievement goals is to work harder, faster, longer, and with more hostility. Thus, they differ from Type B people, who have accurate self-evaluations of their excellences and weaknesses, and who feel that, within the possible paradigm their qualities permit, they are working and doing as best they can. They rarely feel any harrowing need to senselessly accelerate their actions against ever more bitter and aggressively competitive "enemies."

The process of encouraging Type A postinfarction subjects to face up to the realization that perhaps not all their personal qualities are super and that, as a consequence, many of their expectations may be monstrously exaggerated and unreal is not easy. But until the expectations of a Type A postinfarction person are pared to a level of reality, the intensity of Type A behavior cannot be significantly reduced. A postinfarction patient carrying an obstructed coronary artery and an infarct with surrounding tissue prone to arrhythmias cannot be considered as someone other than who he really is, a "cardiac cripple." This may be a harsh conclusion but every postinfarct subject has been dealt a harsh blow which, I believe, in great measure stemmed from his persistent refusal to accept the reality of his limitations.

6. Restructuring of the environment.

Postinfarction subjects can be counseled to eliminate from their schedules all those trivial events in which they previously participated solely (but vainly) to bolster their insecurity and appease their sense of time urgency. Thus, events which chiefly involve persons, such as committee meetings, cocktail parties, games of chance, group discussions, should be examined carefully and eliminated if they do not lift the spirit and do not enhance security and self-esteem.

Similarly, all persons who elicit the free-floating hostility of the Type A personality should be absolutely avoided. For example, a number of our RCPP postinfarction subjects became positively violent in their hostile reactions to a particular television personality who serves as a sports commentator; they were urged to forego the irritating experience—yet a number of them did appear to seek out his program in order to vent their fury on him.

Our patients were given guidelines advising them to avoid hostile persons and unpleasant events and encouraging them to socialize with amiable persons, participate in cultural events, and enjoy the beauty of nature in all seasons in order to raise their spirits and enrich their daily living.

7. Search for the "things worth being."

While all of us, from our high school days on, have sought to obtain the "things worth having," we have not all continued to search for the "things worth being." Thus, while it is eminently worthwhile to own a Wyeth painting or drawing, it is more worthwhile to enhance one's knowledge of American art. A guard at the Metropolitan Museum of Art, watching over the paintings of Pisarro, Renoir, and Monet, now "possesses" these paintings almost as completely as their former owners.

Our Type A post-infarction patients have been so intent on acquiring material objects that their conscious personalities have almost completely overshadowed the unconscious spiritual side of their personalities.

Accordingly, we counseled our patients to reacquaint themselves with the activities they had indulged in while in high school and college—drama, literature, music, history, and art appreciation. It was no easy task getting our subjects to read and understand simple essays (such as those of Montaigne) which they had no difficulty in reading or comprehending during their teens. Such exercises were salutory in driving home to our patients the fact that, in their incessant drive to accumulate more and more material in less and less time, they only succeeded in diminishing their total personalities.

8. Substitution of affection for hostility.

The free-floating hostility in almost all Type A postinfarction patients could not be eradicated or even significantly reduced by pointing to it and trying to get the participants to recognize its presence. However, the successful diminution of intense Type A behavior depended on the ease with which our patients began to give and to receive affection, written, verbal, and tactile. We used an aphorism that not only amused but encouraged our patients in their quest: "It takes a dozen acts of affection to substitute for one of hate." Progress was slow!

9. Drills.

In attempting to diminish the intensity of Type A behavior among our RCPP participants, it was not enough to point out the errors described and their mode of correction. Frankly, their impatience and easily induced hostility were ingrained habits remaining to tyrannize them. If we remember how irritating and upsetting it may be to open a door whose lock is at the left side, to turn the left faucet of a sink and get cold instead of the expected hot water, or to drive on the left side of a two-directional London street, it is easy to understand why habits far more deeply ingrained proved so difficult to eradicate or change.

There is only one way, however, to extirpate these habits which sustain the sense of time urgency and hostility. Shakespeare expressed this method succinctly when he had Hamlet beg his mother to mend her adulterous ways and to abjure the bed of his father's murderer with this advice:

> Refrain to-night;
> And that shall lend a kind of easiness
> To the next abstinence: the next more easy;
> For use [drill] almost can change the stamp of nature,
> And master ev'n the devil or throw him out
> With wondrous potency.

William James also knew the need for drills to eradicate ingrained habits: "There is no more valuable precept in moral education than this, as all who have experience know: if we wish to conquer undesirable emotional tendencies in ourselves, we must assiduously and in the first instance, *cold-bloodedly,* go through the *outward* movements of those contrary dispositions which we prefer to cultivate. The reward of persistency will infallibly come . . . This is recognized by all psychologists, only they fail to see its full import" (21). I am not certain that contemporary psychologists recognize what appeared so obvious to James well over 90 years ago.

Theodore Roosevelt, neither poet nor psychologist, also recognized the potency of "drill," writing in his youth, "There were all kinds of things of which I was afraid at first, ranging from grizzly bears to mean horses and gunfighters but, *by acting as if I was not afraid,* I gradually ceased to be afraid."

Admittedly Shakespeare, James, and Roosevelt make a disparate team of instructors, but their remarks served as an unfailing source of encouragement as we strove to get our participants to engage in the necessary drills. We coached them in walking, talking, and eating more slowly. We drilled them to wait in long lines at banks and supermarkets with equanimity. We admonished them to drive in the slowest lanes of highways in order to rid themselves of their sense of time urgency. Similarly, we demanded that our participants engage in "drills" to diminish their hostilities. Such "cold-blooded" drills consisted of (a) learning to smile frequently; (b) paying compliments and voicing cheerful remarks, not only to their superiors and peers, but also to their subordinates, members of their families, acquaintances, and even to passersby; (c) dispatching small presents (books, flowers) and notes of affection to spouses, children, and close friends; (d) deliberately refraining from correcting the possible errors of omission or commission made by family, friends, or business associates. In respect to this last drill, we found participants ready to do it once they began to recognize that they had resorted to the insistent demand for perfection in others chiefly because of their own deep-seated inadequate self-esteem.

No one recognized more clearly than our participants that whatever reduction in Type A behavior they accomplished was due to their own faithful participation in these drills—which may appear supercilious and ridiculously naive at first.

10. Self monitoring: creating a vigilant internal monitor.

Creation by the participant of an internal monitor who will detect and encourage the eradication of any tendency to revert to the typical manifestations of the original Type A behavior was a cardinal goal of our counseling program. The time would come when they would be expected to fend for themselves. The active presence of this internal monitor would represent our imprint on our participants.

Of course, the internal monitor actually represented our attempt to foster self-talking and self-admonition. "You are talking too much, begin to listen"; "You are walking too fast"; "You are eating too fast"; "You should not have criticized your son for such a trivial error"; "You are trying to do too many things at one time"; "Quit losing your temper at that car driver; after all, his worst fault is that he drives as aggressively and impatiently as you do"; "Since you can't outcompete this man, try to proffer him affection"; "Actually, you are taking this event and yourself far too seriously; relax and, by the way, try to see yourself sometimes as rather ridiculous."

Those postinfarction participants who exhibited the greatest progress in reducing the intensity of their Type A behavior almost invariably were those who had developed an internal monitor that functioned frequently (sometimes as often as 20–30 times a day) and was obdurately immune to the rationalization so often dredged up by the unconscious pull of their old habits of impatience and hostility.

Results

Baseline Characteristics of Participants. The entry characteristics of the randomized Section 1 and 2 participants were almost identical (16). Their average Peel Index was approximately 9.0. About 18% of Section 1 and 2 participants had had two or more myocardial infarctions; 56% had a family history of CHD; 74% were smokers; 40% were hypertensives; 36% suffered attacks of angina; 10% had experienced one or more bouts of congestive heart failure; 26% had undergone coronary bypass surgery, and 2% exhibited arrhythmias. Approximately 98% of these Section 1 and 2 participants exhibited Type A behavior as detected by the VCI.

Although Section 3 participants did not volunteer for group counseling and, therefore, were not subject to randomization, their entry characteristics were found to be essentially the same as those of Section 1 and 2 participants. Of particular interest to us was that participants who had not volunteered for group counseling also exhibited a greater than 95% presence of Type A behavior. This was not self-selection, because fully half the subjects in Section 3 were unaware of the Type A concept.

Effect of Behavioral Counseling. Our behavioral counseling was unquestionably effective in reducing the intensity of Type A behavior in most of our Section 2 postinfarction subjects who continued to receive and accept Type A behavioral counseling. Thus, at the end of three years, 79% had reduced Type A behavior, whether measured by questionnaire, the VCI, or both. By comparison, reduction in Type A behavior was minimal in members of the two sections who had not received Type A behavioral treatment.

Recurrence. The average annual myocardial infarction recurrence rates (Fig.) were 2.7% in Section 2 (Type A counseling) participants—half that in Section 1 (general counseling) participants (5.4%). Indeed, the recurrence rate in this latter group was essentially the same as in Section 3 (no counseling) participants (5.2%). Thus, the only statistically significant difference ($p < 0.01$) in recurrence rates was that between participants in Section 2 and the other two sections.

Employing the "intention-to-treat" principle

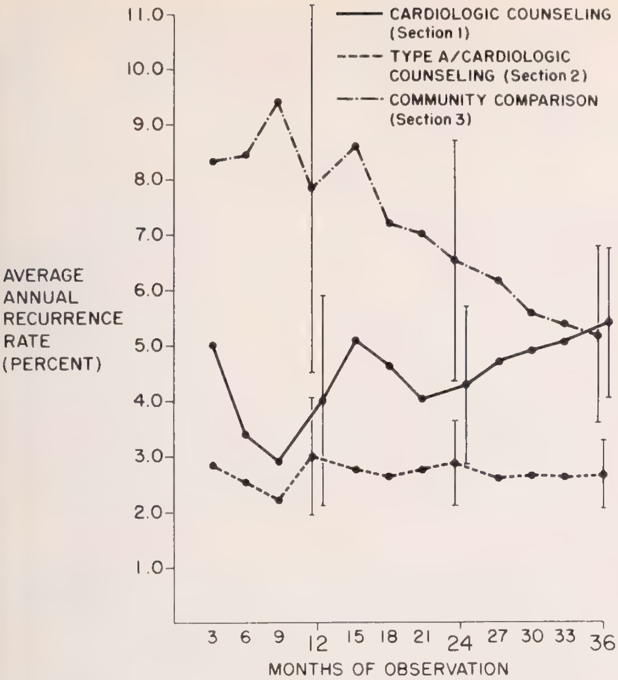

Fig. Cumulative annualized recurrence rate in participants by section, calculated quarterly for 3 years. Note that 95 percent confidence limits (vertical bars) of quarterly recurrence rates of Section 1 and 3 no longer intersect with confidence limit of Section 2 at end of 36 months.

by assuming that everyone initially enrolled in any section still continued in the study (22), this difference in recurrence rate between Section 2 and the other two sections continued to be statistically significant ($p < 0.05$).

Correlation between Behavior and Recurrence. The recurrence data clearly show that postinfarction subjects who had received Type A behavioral counseling suffered significantly fewer recurrent myocardial infarcts than those not counseled. Was this difference directly due to the Type A counseling Section 2 participants received and acted upon?

We believe that it was. When we compared 148 participants who showed significant reduction in Type A behavior at the end of their first year's enrollment in the RCPP, and 326 participants who exhibited no improvement, we found, in the subsequent two years, that the average annual cardiac recurrence rate of the behaviorally improved participants was 1.0%—one-fourth the recurrence rate of the behaviorally unimproved participants (4.3%).

Recurrence and Prior Aortocoronary Bypass. Coronary bypass surgery performed on 255 participants prior to their entry into the RCPP study did not provide greater protection against a myocardial infarct recurrence than the 757 participants who entered the study without such surgery. Thus, the three-year cumulative rate of myocardial infarction was 9.0% and sudden cardiac death was 4.5% in those who had undergone bypass surgery prior to entry, and 8.3% and 4.7% in those who had not undergone such surgery. The baseline data indicates that the bypass participants had suffered two or more infarcts prior to entry more frequently than nonbypass participants and possessed a significantly higher Peel index (17), suggesting the possibility that the participants with bypass on entry had a more ominous prognosis than those without bypass. The Peel index, a number describing the severity of a patient's last acute myocardial infarction, is composed of such items as number of past infarctions and occurrence of shock, congestive heart failure, and serious arrhythmias in the course of the last acute myocardial infarction. It has been found (17, 23) to have considerable importance in the prediction of cardiac recurrence. For example, the five-year survival of postinfarction subjects whose index is 8 or below is almost twice that of subjects whose index is 9 or above. By employing univariate chi-square analyses, we were able to compare the recurrence rates of nonbypass participants entering the study at low risk (no infarct or one infarct prior to entry and a Peel index below 8) and at high risk (two or more infarcts and a Peel index of 9 or above). No significant difference was observed in the recurrence rates of the bypass and nonbypass participants in these two subgroups.

Despite this apparent failure of bypass surgery to protect the total cohort of postinfarction subjects from cardiac recurrence, those bypass participants who were assigned to Section 2 and, thus, received Type A behavioral counseling exhibited a three-year cumulative recurrence rate of only 2.1%. This is well below half the recurrence rate observed in the nonbypass Section 2 participants who received the same Type A behavioral counseling and one-eighth the recurrence rate of Section 1 and 3 bypass participants who received no Type A counseling.

Discussion

I have devoted a substantial part of this report to our counseling procedures, chiefly because, to my knowledge, no cardiology textbook devotes more than several paragraphs at most to the entire subject of Type A behavior—an omission that leads to the graduation of thousands of medical students today who have no knowledge whatsoever about Type A behavior except what they may have picked up from their reading of lay articles dealing with the syndrome.

But I also have expanded on the subject of counseling because it must be done as meticulously as aortocoronary bypass is performed. Whereas the scalpel, scissors, and delicate sutures are the essential tools for bypass, Type A counseling uses only combinations of words, phrases, and sentences and the verbal intonations and gestures of the counselor accompanying these oral combinations.

I must emphasize the extreme importance of the counselor in the Type A counseling process. I am certain that recruiting and training effective Type A counselors is more difficult than recruiting and training surgical residents who will perform excellent coronary artery surgery; certainly in 1977 it was difficult to assemble counselors for the RCPP study. Nor is it easy to find cardiologists, psychiatrists, and psychologists who are interested in counseling coronary patients, well grounded in the humanities, well informed on the clinical and pathophysiologic aspects of CHD, and not so badly afflicted with Type A behavior that it would be medical mockery to have them attempt Type A counseling. In addition, each should have sufficient integrity and courage to point out and then to insist upon the changes necessary in the career of some patients to prevent further heart damage or a lethal myocardial infarction, a personality capable of coping with patients who are frequently hostile, and, finally, the capacity to sincerely care for these difficult patients.

Note that Professors Blankenhorn, Jenkins, and Insull, in an open letter to the editor of the *Annals of Internal Medicine* (24) reported that, in their study of a random collection of cardiologists, they found that all of them were not just Type A, but so "Super Type A" that they recommended that cardiologists no longer allow themselves to treat or advise their coronary patients but rather employ paramedical personnel to do so.

It is because of this difficulty of finding suitable group counselors that I believe the results we observed in the RCPP study will not be too easily repeated. But I don't think it will now take over two decades to assemble qualified therapists to give Type A counseling to postinfarction patients. When this is accomplished, I suspect their protective results will exceed ours. After all, we have only shown the way.

I believe that the truly dramatic reduction in recurrent myocardial infarctions that we observed in coronary bypass participants who were lucky enough to be randomly enrolled in the Type A counseling section deserves some comment. This low rate (0.7% per year), which is eight to nine times lower than that observed in the Framingham Study, can be attributed to the following facts:

First, some participants had, by coronary bypass prior to entry, an increased blood flow to various previously ischemic myocardial areas.

Second, all participants were repeatedly prohibited from indulging in any type of endurance exercise or exertion involving lifting heavy objects or severe isometric diaphragmatic contractions.

Third, all participants were repeatedly warned that their bypass surgery in no way gave them a clean bill of health. They were told that even the proximal coronary artery segments receiving their bypass segments also were diseased and, if the original disease cause was unchecked, it would continue to decrease the lumen of those arteries. Other coronary arteries seen to be relatively potent at the time of their last angiographic examination were subject to the ravages of their progressive disease.

Fourth, all participants were reminded again and again that, despite their bypass surgery, their hearts carried a scar plus abnormal surrounding tissue which is irritable and subject to triggering dysrhythmias, such as ventribular fibrillation and cardiac standstill. Bearing this potential time-bomb, our subjects were instructed to avoid activities (severe exertion, prolonged emotional exhaustion, a single heavy meal) which may provoke a heart attack. They were reminded that one episode of irritation and anger quickly snuffed out the life of that great surgeon, John Hunter, in 1793.

Fifth and finally, all participants were given Type A counseling designed to prevent, as much as possible, chronic elevations in the blood level of various hormones—norepinephrine, ACTH, and testosterone—implicated in the disease process.

The results observed in this study revealed that Type A behavior from moderate to severe was present in virtually all male and female postinfarction subjects under the age of 65 years. It was the only one of all currently suspected coronary risk factors that was found to be present in essentially every patient. Type A behavior was modified in the majority of postinfarction subjects

(79%) who continued in the RCPP study for three years. And—most important—modification of Type A behavior led to a marked reduction in recurrent heart attacks.

When all three of these observations are considered, I believe that the conclusion is inescapable: Type A behavior is now a proven cause for the accelerated development of coronary heart disease and when modified, the course of the disease can be significantly altered. At the present time, the causal status of no other coronary risk factor has been similarly documented, nor has the alteration of any other coronary risk factor been demonstrated to lead to any change in the course of established CHD.

I am gratified that so many of my colleagues in psychiatry, clinical psychology, epidemiology, surgery, and cardiovascular medicine have now embraced the thesis that Type A behavior plays a central role in the pathogenesis of CHD—which we first suggested more than a quarter of a century ago (1).

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Aging, Stress, and Sudden Cardiac Death

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Abstract

Cardiac arrhythmia leading to sudden death is a common disease of middle age, but its impact on the survival and function of older adults has been largely ignored. This is in spite of the facts that (a) cardiovascular diseases already complicate or account for 25% of the dementias; (b) as many as half of all sudden deaths occur in individuals 75 years or older; and (c) 30%–50% of those resuscitated are left with significant cognitive deficits. Age-related stressors (bereavement, social isolation, retirement dissatisfaction, changes in major life events, and household size) have been empirically linked to cardiovascular mortality, and there is reason to believe that the unifying emotional result of these stressors is episodic depression. We studied 88 patients during acute treatment for life-threatening arrhythmia. Follow-up mortality was significantly related to depression and cognitive impairment found at initial assessment. Impairment correlated with measures of depression, functional status, heart failure, and ventricular tachycardia, but not arrhythmia severity or treatment efficacy. Our results from middle-aged adults suggest that therapeutic advances that increase the number of arrhythmia survivors may proportionately raise the percentage of vascular dementia cases in the elderly and that some degree of the observed morbidity and mortality may be a manifestation of depression and dementia. If confirmed, these findings would also indicate that psychosocial interventions, in addition to biomedical advances, will be needed to maximally reduce sudden cardiac mortality and arrhythmia-related morbidity. We suggest that psychosocial interventions for patients at risk for sudden death focus on (a) reduction of age-related stressors through (b) aggressive treatment of depression and (c) early identification of and preparation for the behavioral sequelae of cognitive impairment.

In this paper we argue that stressors related to the social, psychological, and biological consequences of aging are implicated in both the precipitation and progression of life-threatening arrhythmic disease. Preliminary evidence from studies of middle-aged adults indicates that the principal age-related risk factors for sudden cardiac death are depression and cognitive impairment. With this evidence in mind, we can tentatively formulate psychosocial interventions to reduce the morbidity and mortality associated with arrhythmias of sudden cardiac death in the elderly.

Cardiac arrhythmia leading to sudden death is the leading cause of nonaccidental mortality in adults less than 65 years of age. It claims 450,000 lives each year, accounting for two-thirds of the 700,000 annual deaths due to heart disease in the United States (1). It frequently strikes without warning and leaves 30%–50% of those resuscitated with significant cognitive deficits (2). Though it is a common cardiovascular disease of the young and middle-aged, its impact on the survival and functional effectiveness of older adults has been largely ignored. This is in spite of the fact that as many as half of all sudden deaths occur in individuals aged 75 years or older (3).

Unlike ischemic heart disease, in which the

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identification of both biomedical and psychosocial risk factors has lead to a 30% reduction in mortality over the last 20 years (4), there are as yet no identifiable predictors of sudden death other than previous ischemia and arrhythmia (5). Moreover, as many as 50% of sudden deaths occur in individuals prior to the development of signs or symptoms of ischemia (6). Thus, if ischemic disease could be completely prevented, sudden cardiac death would remain a substantial health problem (7). Since the biological indicators of risk for sudden death are of little predictive value until cardiac output and rhythm are both substantially and independently impaired, the search for behavioral risk factors is particularly important (8).

Depression

Evidence suggests that depressive symptoms, as opposed to other emotional states (9–12), may be the principal unifying experience by which diverse psychosocial events lead to an increased risk of sudden death. Life stressors, including bereavement (13, 14), social isolation, dissatisfaction with work or retirement (15), and major changes in life events (16–18) and household size (19), have been empirically linked to overall cardiovascular mortality or to sudden cardiac death. After adding cognitive impairment to bereavement, retirement, and change in household size, we arrive at a set of factors that are chronologically related to aging. The behavioral, emotional, and psychological mechanisms by which these stressors generate cardiovascular effects in aging individuals require further investigation.

Interaction of the catechol-corticoid systems presents a plausible physiologic mechanism by which depression contributes to cardiovascular mortality. Although biochemically heterogeneous, depressive disorders share a common domain of neurohumors (catecholamines, serotonin) and hormones (cortisol, thyroxine) that wax and wane with the course of the disorder. Alterations in the catecholaminergic system, including catecholamine concentrations and receptor sensitivity, have recently been described in depression (20). In addition, the catecholaminergic system has been considered for a number of years to be important in the etiology and treatment of ischemic and arrhythmic disease. An acute catecholamine surge in part accounts for the frequency with which malignant arrhythmias appear during the first hours following myocardial infarction (21). Conversely, the serotonergic system, long thought to play an important role in depression, has also recently been implicated in arrhythmias (22).

Cortisol, which is elevated in 50% of patients suffering a major depressive episode (23), has been experimentally shown to worsen the destruction of cardiac tissue caused by catecholamine excess (24). Enzymes responsible for the synthesis and degradation of catecholamines are regulated by cortisol, which also enhances the heart's catechol receptor sensitivity so that the net effect of hypercortisolemia is an amplification of catecholamine activity (25). Cortisol also elevates blood pressure, serum lipids, and glucose, all established risk factors for ischemic disease. More recently, Sapolsky and Pulsinelli (26) have shown in the rat that cortisol potentiates neuronal degeneration due to both age and experimental brain ischemia.

Cognitive Impairment

This brings us to cognitive impairment, which, after depression, is the second major age-related contributor to cardiovascular mortality. The memory impairment and slowed mental performance associated with cardiovascular diseases are thought to result from either multiple small strokes due to microscopic infarctions or from large-scale cerebral ischemia due to major vascular accidents (27). However, the interaction of cardiac output, metabolism, arteriosclerosis, and the autoregulation of cerebral blood flow are far more complex than this simple dichotomy implies (26). Numerous reports suggest that arrhythmias may occupy the middle ground (28, 29). Moreover, cognitive impairment has repeatedly been shown to predict early mortality following surgical treatment for ischemic and valvular heart disease (30, 31).

Studies of mental status following resuscitation from cardiac arrhythmia and arrest provide convincing evidence of a high prevalence of cognitive deficits (32, 33). Reich et al (34) have described in detail the social and emotional significance of unrecognized or misdiagnosed cognitive impairment in sudden-death survivors. However, lack of data on the presence, progression, and clinical significance of impairment in the larger group of arrhythmia survivors who have not required resuscitation may have led to an underestimate of the problem's importance. The issue is critical for hypotheses of age-related sudden-death stressors in light of the epidemiologic features of the population at risk.

Dementia (insidious, progressive cognitive

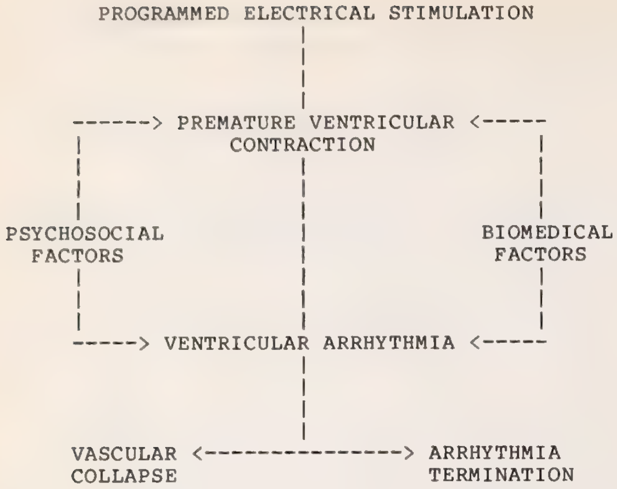

Fig. Hypothesized interactions between biobehavioral factors thought to mediate genesis and activity of ventricular arrhythmias. In our model a programmed electrical stimulus is used to activate a premature ventricular contraction (PVC) which precipitates ventricular arrhythmia (tachycardia or fibrillation) followed by arrhythmia termination or cardiovascular collapse and resuscitation. In nature, activators of PVCs are poorly perceived and mediators of termination are as yet unknown.

impairment) is currently associated with a lifetime risk somewhat greater than one in four (27), and the numbers of persons at greatest risk for dementia, those older than 65, will more than double over the next 50 years. In contrast, the lifetime risk of a heart attack (with 1.5 million attacks each year in the United States) is estimated to be one in five (35). Although more than 50% of all cases of dementia are attributed to Alzheimer's disease, the importance of primary neuronal degeneration of the Alzheimer type may be less than currently estimated (36). Other etiologic factors leading to a secondary dementia may be more amendable by early intervention, provided we identify the modifiable risks. Vascular conditions, including arrhythmias, which account for 25% of all dementias, represent the largest category of such factors. Finally, the potential effect of impaired cognition, whether progressive or not, on therapeutic compliance is substantial. Up to 70% of patients who report good compliance with antiarrhythmic medication are found to be in the subtherapeutic range (37, 38). The importance of recognizing the potential contribution of dementia to the morbidity and mortality of life-threatening arrhythmias is obvious.

From the evidence presented above, it follows that the principal age-related risk factors for sudden cardiac death are depression and cognitive impairment. Unfortunately, the methodological problems of rigorously testing such hypotheses are formidable (39). Attempts to model the biobehavioral mediation of sudden death through animal studies, post hoc analyses, and divergent naturalistic and experimental settings have not added to the prediction of human risk (40–46). Investigators of psychophysiologic, psychosocial, and neuroendocrine factors have been forced to focus on the spontaneous occurrence of premature ventricular contractions, which are variably predictive of arrhythmia risk (47). Until recently, the ability to reliably manipulate arrhythmia with readily quantified stimuli and to minimize the spontaneous variability of arrhythmia onset has been lacking (48, 49).

Programmed Electrical Arrhythmia

The clinical induction of arrhythmias by programmed electrical stimulation by Wellens (50) in 1967 has provided a unique opportunity to overcome these difficulties. Programmed stimulation is used to test treatment efficacy in patients known to be at risk for sudden death due to recurrent arrhythmia (51–53). It has gained widespread acceptance among major cardiology centers (54–58).

We are currently attempting to disaggregate the biobehavioral determinants of sudden death from our studies of programmed stimulation patients. In our model (Fig.) psychosocial, behavioral, catechol, and corticoid measures are set as independent variables, and the quantity of electrical stimulation required to overcome the ventricular threshold and induce and terminate arrhythmia is analyzed as a dependent variable. This work requires the specialized resources of a major electrophysiologic Arrhythmia Service which cares for large numbers of patients. The Arrhythmia Service generates a biomedical database from which all known predictors of sudden death can be measured with a high degree of accuracy (59). Furthermore, since the patient's preexisting arrhythmia is induced in a drug-free, unsedated state, and in the controlled environment of a cardiac catheterization laboratory, the influence of behavioral variables can be assessed immediately without the need to wait for the spontaneous emergence of arrhythmia.

In 1985 we reported results from our preliminary investigations of depression, cognitive impairment, and survival in 88 patients with life-threatening supraventricular and ventricular tachycardia and fibrillation (60–62). Patients were evaluated with Kimball's (63–66) global assessment method for adjustment, dependency,

TABLE 1

Arrhythmia Severity Criteria

	Grade
Spontaneous Arrhythmia*	
Premature Ventricular Contraction	
No extrasystoles	0
Isolated, <30/hr	1
Isolated, >30/hr	2
Multiform, multifocal	3
Repetitive, couplets	4a
Repetitive, 3 or more (salvos)	4b
Interrupts or abuts T wave	5
Induced Arrhythmia†	
Not inducible	1
VP + 3 PES or BRVP or "Ramps"	2
3 PES or VP + 2 PES	3
1 or 2 PES or VP + 1 PES	4
Termination	
No tachycardia	0
Spontaneous	1
PES or VP	2
Spontaneous prior to DCCV	3
DCCV	4

PES, extrasystoles induced by programmed electrical stimuli; VP, ventricular pacing; BRVP, bursts of rapid ventricular pacing; "Ramps", pacing with continuously increasing rate over several seconds; DCCV, direct current cardioverting shock to chest.

* Assessed noninvasively from 24-hr monitoring or modified exercise testing.

† Assessed invasively by electrophysiologic pharmacologic study.

TABLE 2

Characteristics of 88 Patients Clinically Evaluated with Programmed Electrical Stimulation and Psychiatric Interview

		SEM‡
Admission		
Age in years mean	52.2	1.60
Sex (male:female)	54:34	
Socioeconomic class (1–5) mean	3.10	0.10
Diagnosis		
Ventricular tachycardia/fibrillation	66/88	
Supraventricular tachycardia	12/88	
Other*	10/88	
Cognitive impairment	15.7%	
Psychological profiles†		
Depressed	9%	
Anxious	25%	
Dependent	17%	
Adjusted	49%	
NYHA functional class (1–4) mean	1.56	0.09
Noncardiac class (1–4) mean	1.24	0.08
Killip's cardiac performance class (0–4) mean	1.92	0.09
Discharge		
Psychological profiles†		
Depressed	5%	
Anxious	20%	
Dependent	21%	
Adjusted	54%	
Follow-up (mean at 18 mo)		
Rehospitalization, all causes	60.7%	
Mortality, all causes	17.2%	

* Psychiatric conversion reaction, syncope of unknown origin or associated with valvular heart disease.

† Kimball's global assessment method; inter-rater r = 0.81.

‡ standard error of the mean.

anxiety, and depression and with Jacob's (67) Cognitive Capacity Screening Exam. Biomedical assessment consisted of noninvasive (spontaneous) and invasive (stimulated) arrhythmia severity criteria (Table 1) and measures of New York Heart Association functional class and cardiac performance (heart failure). New York Heart Association functional class is the major biomedical predictor of mortality in this population. Data on mortality and rehospitalization were collected over a mean period of 18 months during clinical follow-up by the Arrhythmia Service (Table 2).

The depressed group was found to have greater impairments in cognition, functional class, and cardiac performance measured at admission and disproportionate mortality at follow-up, in spite of significant therapeutic reduction in

TABLE 3

Associations Among Selected Variables

Variables	r	p
Depression × dementia	0.29	0.005
Depression × NYHA functional class	0.26	0.05
Dementia × mortality	0.21	0.05
Depression × mortality	0.21	0.01
"Noncompliance" × mortality	0.19	NS
15 arrhythmia parameters × 4 psychological categories	—	NS

TABLE 4

Correlates of Cognitive Impairment in 88 Patients Evaluated with Programmed Electrophysiologic Studies and Psychiatric Interview

	r	p
Age	0.38	0.0005
Noncardiac functional class	0.45	0.0005
Killip's congestive failure class	0.44	0.0005
NYHA functional class	0.41	0.001
Coronary artery disease etiology	0.28	0.01
Mortality	0.21	0.05
Ventricular tachycardia-fibrillation diagnosis	0.21	0.05
Mean extrasystoles per hour	0.15	NS
Arrhythmia grade from 24-hr monitored sample	0.05	NS
Arrhythmia grade from exercise test	0.13	NS
PES induction criteria	0.04	NS
PES termination criteria	0.16	NS
Number of cardioversions this admission	0.02	NS

arrhythmia severity. This would be trivial were it not for the observed lack of differences in arrhythmia severity among the four Kimball groups (adjusted, dependent, anxious, depressed) and for the significantly greater percentage of depressed patients who died.

Cognitive impairment was found in 15.7% of the 88 patients. However, for the 66 ventricular tachycardia and fibrillation patients, those at highest risk for sudden death, the frequency was 21.2%. More important, both cognitive impairment ($p < 0.05$) and depression ($p < 0.01$) correlated significantly with mortality (Table 3). Other correlates of cognitive impairment are shown in Table 4.

Regression analysis was performed to prioritize the contribution of all significant variables, including cognitive impairment and depression, to the variance in survival. The first priority variable was New York Heart Association functional class, accounting for 24.4% of the variance. The next largest contributor to the remaining variance was cognitive impairment, which accounted for 10.7%. Thus cognitive impairment ranked higher than all but one of the cardiovascular variables in the prediction of mortality.

Summary

Mortality and morbidity from sudden cardiac death cannot be fully reduced by the current level of biomedical technology for several reasons. First, sudden death is the initial sign of ischemic heart disease in a large proportion of individuals and there is as yet no identifiable risk profile short of preexisting ischemia and arrhythmia (6). Even if ischemic disease could be completely prevented, sudden cardiac death not associated with arteriosclerosis would still be a sizable problem (7). Second, experience has shown that geographic factors, hospital proximity, and resuscitation team arrival time will continue to affect recovery and cognition even in well-organized community programs (68, 69). Mobile resuscitation teams and innovations in the electrophysiologic-pharmacologic management of arrhythmias promise to increase the absolute number of survivors but not necessarily the quality of survival. Therapeutic advances that increase the number of arrhythmia survivors may proportionately increase the percentage of vascular dementia cases (62). Third, arrhythmic death and disability may in part be a function of depression and progressive cognitive deterioration, which lessen the capacity to comply with treatment, to maintain a stable social and physiologic milieu, and to continue an adaptive emotional life.

We suggest that psychosocial interventions for patients at risk for sudden death focus on (a) the reduction of age-related stressors through (b) the aggressive treatment of depression and (c) early identification of and preparation for the behavioral sequelae of cognitive impairment. Controlled clinical trials to test the power of these interventions, similar to Friedman's (70) effort to alter coronary-prone personality characteristics in ischemic disease patients, will remain premature until the relationship between the stressors and arrhythmic disease is more fully defined. Experimental designs based on the use of programmed electrical arrhythmia stimulation offer an untested opportunity to both define and confirm the biobehavioral mediators of sudden death.

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Stress and the Lung: Hypersensitivity of Airways, Neurogenic Pulmonary Edema, and Hyperventilation Syndrome

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Respiration has been defined as the process by which living things obtain and use oxygen (1). In the human, oxygen is inspired and metabolized by the body. Carbon dioxide is formed in the body during metabolism and is exhaled into the atmosphere. Respiration requires the subject to undergo biological adaptation to the environment. The mechanisms of biological adaptation are physiologic and psychological (2). The respiratory system is sensitive to mechanical, chemical, and emotional influences.

Stress is a body condition that can occur when a person faces a threatening or unfamiliar situation. Respiratory stress is a change in lung functioning that results from a life change (2). The response of a person to this respiratory stress will depend first on what social supports are available to the individual, such as being loved, being esteemed, being part of a mutual defense system. Second, it will depend on the person's coping ability or ability to change the environment to meet one's needs. Third, it will depend on adaptive ability or the ability to adapt oneself to the existing environment. Finally, the pathophysiologic state of the stressed individual will affect the person's response to stress.

Bronchial Asthma

For many years physicians have been impressed by the influence of psychological stimuli on bronchial asthma (3–7), a pulmonary disease characterized by intermittent episodes of bronchospasm (reversible airway obstruction). Most asthmatic patients are young, often under 45 years of age, and they often have a personal or family history of allergy or atopy. From a psychiatric point of view, asthmatic attacks have been felt to represent the repressed cry for the mother (8). Asthmatic patients often have an exaggerated dependence on their mother, and anything that tends to sever this close relationship between the patient and the protection of the mother frequently results in an asthmatic attack.

A study of the interrelationships between the psychological and physiologic aspects of bronchial asthma by McFadden and colleagues in the mid-1960s at the Downstate Medical Center in Brooklyn, New York (9–11) brought provocative results that confirmed the beliefs of many older investigators.

Forty patients with bronchial asthma—10 normal, 15 with restrictive disease, and 15 with bronchitic disease—were studied. All were told that they would inhale five increasing concentrations of an irritant or allergen which they said had caused previous illness. The substance that was given was normal saline. Plethysmographic measurements of airway resistance (Ra) and thoracic gas volume (TGV) were measured, and the reciprocal of Ra, conductance (Ga), was related to TGV to give a Ga/TGV ratio. This Ga/TGV ratio must be known because Ra and Ga have no meaning unless one knows at what volume they were measured. Five successive measurements of each variable were made at each point in the study.

Baseline data (Ra, TGV, and Ga/TGV) were

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obtained in all patients prior to any inhalations. Over a 30-sec period, 10 deep breaths of suggested allergen or irritant were inhaled from a nebulizer. In fact, saline was given. Ra, TGV, and Ga/TGV ratio were measured at 1 and 4 min after inhalation. If wheezing or dyspnea occurred, the test was stopped and the patient received the placebo form of saline, but the patient was told it was isoproterenol, a potent bronchodilator. After 3 min the Ra, TGV, and Ga/TGV ratio were measured.

The control group of normals, patients with restrictive disease, and patients with bronchitis did not respond to the suggestion, as evidenced by a lack of change in their Ga/TGV ratio. In the asthma group, 21 patients failed to respond to the suggestion, but 19 did. Twelve had an actual clinical asthmatic attack, and 7 significantly lowered their Ga/TGV ratio. At this point the 19 patients were given a last inhalation of bogus allergen or irritant which they were told was an almost pure allergen or irritant. The material actually inhaled was isoproterenol. There was no improvement, but a decrease in Ga/TGV ratio occurred, so that suggestion really negated the pharmacologic effects of isoproterenol. Next the 19 patients who responded significantly to the suggestion received the nebulized saline placebo again and were now told it was isoproterenol. All had a significant improvement in their Ga/TGV ratio.

In a subsequent study of 5 of the most suggestible asthmatic subjects, these experiments were performed after atropine blockade of the vagus nerve (10). Under this circumstance the bogus allergens or irritants which were normal saline had no effect on airway caliber and the Ga/TGV ratio was unchanged. When the effect of the atropine wore off, these exquisitely sensitive patients once again responded to the bogus allergens or irritants with a reduction in Ga/TGV ratio.

The authors pointed out that the changes in Ga/TGV ratio were due to a fall in Ga. The changes in Ga/TGV ratio were so rapid and reversible that their cause appeared to be an alteration in smooth muscle tone. The ability of atropine to prevent the response suggested that postganglionic cholinergic efferent fibers were blocked by this drug. The potency of suggestion as a factor in bronchomotor tone was illustrated by the response to isoproterenol, wherein suggestion negated the pharmacologic effect of the drug, and symptoms were not reversed until the patients thought they were getting the drug. The clinical significance of suggestion in asthma can be inferred because in no other common disorder have so many therapeutic approaches been employed with reputed success. Any assessment of treatment success must include an appraisal of the role of suggestion. If an asthmatic patient associates a specific stimulus with the onset of an attack, known contact with that stimulus will cause an attack, whether or not that agent is physiologically active. Furthermore, if a patient expects a good effect from a specific form of therapy, the treatment is likely to be effective.

In view of these data, it becomes obvious that approximately 50% of adult asthmatics can have their airway resistance changed for better or for worse with suggestion alone. Any physician who has cared for these patients is not surprised by these findings, because management of asthmatics requires not only the science of medicine, but also the art. The kind, benevolent physician who cares for these patients can reinforce the effectiveness of the medication by stressing to the patient that improvement will occur. This positive attitude on the part of the doctor will produce positive results in a great number of asthmatics (9–11).

Neurogenic Pulmonary Edema

Another abnormality associated with stress is neurogenic pulmonary edema (12–14). In this malady, pulmonary edema occurs after a central nervous system (CNS) insult such as a grand mal seizure, subarachnoid hemorrhage, intracerebral hemorrhage, head trauma, operative trauma, hydrocephalus following bacterial meningitis, or intracerebral tumor. It has been suggested that a pulmonary endothelial permeability defect occurs in this edema, as well as pulmonary venoconstriction which causes an elevation of pulmonary capillary wedge pressure.

Theodore and Robin (12, 13) suggest that this edema results from a massive adrenergic release from the CNS (possibly the hypothalamus) which results in severe pulmonary and systemic vascular hypertension in the early phase (in seconds to minutes). This results in a profound increase in systemic vascular resistance with an extensive shift of fluid from the systemic to the pulmonary circulation. The resulting pulmonary edema is associated with pulmonary hypervolemia, high pulmonary hydrostatic pressure, and pulmonary vascular injury. In the second phase, systemic and pulmonary vascular pressures return to normal, but pulmonary edema persists owing to pulmonary vascular injury, and the edema fluid has a high protein content.

This edema is associated with a high-pressure insult and a pulmonary endothelial permeability defect. These two abnormalities most likely arise via different mechanisms, but their combined effect is synergistic with accumulation of extravascular lung water and pulmonary edema.

Management of this edema is essentially supportive. However, as its severity increases and hypoxemia becomes more abnormal, the use of supplemental oxygen, mechanical ventilation, and also control may be not just helpful but lifesaving. Positive and expiratory pressure (PEEP), which is so useful in noncardiogenic pulmonary edema, must be used with extreme caution in this disorder because PEEP decreases cerebral venous outflow and increases intracranial pressure. These can all result in further neurologic deterioration and finally death of the patient.

Hyperventilation

Hyperventilation syndromes are usually associated with action-oriented behavior (2). This respiratory hyperfunction may result from an affective disposition to anger, anxiety, euphoria, or related emotional states. This increase in ventilation is often in preparation for escape, alleviation, or removal of stressful stimuli, or to engage in pleasurable pursuits.

Summary

Physicians must increase their awareness of respiratory psychobiological factors that influence an individual's ability to breathe. Study of physiological changes and their consequences cannot be examined by themselves but must be integrated with the multitude of psychological factors that affect the total person. It is the combined observation of the physiologic, psychologic, and environmental factors that allows the clinical doctor to see the whole problem and thereby institute proper and complete therapy. Bronchial asthma, neurogenic pulmonary edema, and hyperventilation are but a few situations that are clearly affected by stress.

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Stress and the Gastrointestinal Tract

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The term "stress," in use in the English language since the 15th century, has come to express a number of mechanical, emotional, and biological ideas. In psychophysiologic terms it was at one time confusingly thought of as an environmental factor, the response of the individual, or an interaction of the two.

Selye clarified matters by defining the "stressor" as the environmental factor, an external cause or stimulus (anything which produced stress), and "stress" as the response of the individual, the state of induced disequilibrium (1). He further defined three stages of stress: alarm reaction or mobilization of bodily defenses, associated with pituitary and adrenal secretions and involution of the thymus; resistance, associated with "adaptive energy," elevation of cortisol secretion, and a dramatic reduction in the alarm reaction processes; exhaustion. Implicit in this description and later, better definitions were that stressors could be good or bad, acute or chronic, that there are degrees of stress, and that stress could be moderated in various ways.

Biology of Stress. In the years since Claude Bernard, Cannon, and Selye, the central role of the hypothalamus and other neurohumeral mechanisms in the body response to stress have been demonstrated. A wide variety of stimuli, from anxiety, pain, and exercise to trauma, infection, burn, starvation, exposure to cold, and myocardial infarction have been shown to elicit similar responses. They are modified by the magnitude of the stress and such factors as age, sex, situational status, physical condition, and preexisting disease. The reactions are characterized, in general, by an increase in adrenergic activity, increased energy requirements, and a shift of body substrates from storage to use.

Afferent and lumenal stimuli are integrated in several hypothalamic nuclei and lead to largely sympathetic and motor efferent responses (2). Epinephrine is released from the adrenal medulla and norepinephrine from the sympathetic nerves (3). Corticotropin-releasing factor is discharged from the hypothalamus, reaches the pituitary via its portal circulation. The anterior pituitary then releases ACTH (4). Catecholamines also appear to be capable of releasing and regulating ACTH. ACTH, glucocorticoids, neuronal activity, in turn, effect the synthesis of epinephrine by influencing the activity of catecholamine biosynthetic enzymes. CRF stimulates endorphin release as well as ACTH from the anterior pituitary. Growth hormones and prolactin are increased, and testosterone is decreased as a stress response (5). The fight-or-flight response is characterized by sympathetic discharge with tachycardia, pupillary dilatation, piloerection, tachypnea, and increased muscle blood flow. Several gut peptides with possible inhibitory effects on intestinal motor activity are also released by stress, including gastrin, glucagon, neurotensin, motilin, and pancreatic polypeptide (6). Glycogenolysis is stimulated via several mechanisms. Decrease in glucose tolerance, increase in free fatty acids, and a variable nitrogen balance are commonly seen in stress (3).

Immunological changes occur, some attributable to the humeral discharge and others which remain to be clarified (7, 8).

Measures of Stress. Research in stress, largely in animals, has often centered around a number of stressor models, including restraint, cold restraint, forced exercise, burns, fasting, heat, cold, hemorrhagic shock, sepsis, trauma, and electric shock. The more compassionate human studies

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have used spontaneously occurring illness and injury and some "gentler" stressors such as the stress interview or the cold pressor test.

A large number of human studies have attempted to relate social factors, psychopathology, and stressful life events to illness as a measure of stress. This type of study was derived from the early works of Walter Cannon (9), who observed bodily changes in relation to emotional changes, and Franz Alexander (10, 11), who related personality characteristics to selected syndromes and developed the psychosomatic theory. They were formalized by Holmes and Rahe and associates initially in a 43-item check list, and later in a weighted but similar questionnaire, the Social Readjustment Rating Scale (12). The results of the latter, scored as life change units, implies that the amount of readjustment required determines the stressfulness of the event.

Psychiatric diagnostic interviews, recently utilizing the Diagnostic Interview Schedule, Version 3 (13), a structured directed interview that establishes diagnoses according to the widely accepted Diagnostic and Statistical Manual of Mental Disorders, 3rd edition (14), has been used in an attempt to relate psychiatric disease and, by implication, stress, to specific illnesses. Psychometric inventories (15–20) have been used.

Some of these approaches have been criticized for being subjective, simple, and conceptually deficient, for demonstrating the consequences rather than the causes of illness (21), and for revealing health-seeking behavior rather than the onset of illness. According to Hudgens, most people do not become disabled even when terrible things happen to them. Exposure to stressors alone is almost never a sufficient explanation in humans for the onset of illness under ordinary circumstances (22).

More objective, but also posing difficulties, are measurements of 17 hydroxycorticosteroids, urinary catecholamines, electromyography, plethysmography, and galvanic skin resistance. More recently, measurements of ACTH, epinephrine, and other substances have been used.

The difficulties relate not only to methodology, but to the complex and ambiguous nature of stress. In its simplest form, stress may consist of any adaptive challenge or task. Implied is that stress may be at times maladaptive and even overwhelming, but may also be normal, healthy, and important in the learning process. Support for the latter is suggested by research in operant conditioning, including studies on avoidance of pain, helplessness (23), and autonomic responses. Lacey and Lacey showed that individuals respond consistently and for years to different stressors with the same profile of autonomic responses. Other individuals respond equally reliably with a different set of autonomic responses (24). Some of these visceral responses may be learned. Forty curarized rats were successfully taught by operant conditioning to increase, and forty others to decrease, their heart rates (25).

Learned visceral responses may be adaptive or maladaptive, and may be an important link between stress and psychosomatic symptoms. Changes in gastric blood flow have been "taught" to rats (25). In humans, using similar techniques, two mentally retarded children were taught to stop ruminative vomiting (26). Of 20 patients with the irritable bowel syndrome, 14 were taught to increase the threshold volume of air in a rectosigmoid balloon required to initiate spastic contractions (27). There are other examples, all suggesting that visceral responses, including symptoms, may be learned and unlearned and that these responses may be adaptive or maladaptive. These links between stress and psychosomatic symptoms provide support to the psychosomatic concept on the one hand and to the validity of therapy, which includes teaching to cope, on the other.

Esophageal Disorders

The possible relationships of emotional factors and esophageal disease has largely centered on chest pain and motor disorders of the esophagus. Clouse and associates reported a correlation between psychiatric disorders and certain contraction abnormalities of the esophagus (28) and between severity of esophageal and psychiatric symptoms (29). The relationship between esophageal contraction abnormalities and chest pain attributable to the esophagus is complex and unsettled. Motility disorders are reported in a varying number of patients with chest pain and normal coronary arteries (30). Clouse and associates found no significant manometric changes and spontaneous chest pains in patients with presumed esophageal spasm (28). Obrecht and associates found that patients with both irritable bowel syndrome and the nutcracker esophagus were likely to respond to psychological stress with an increase in symptom frequency and anxiety and that these disorders have a stress-related component. They and others suggest a relationship between the two conditions (31).

In general, however, the nature and classification of esophageal motor disorders remains confused, as does their relationship to stress, if any.

Ulcers

Peptic Ulcers. The association of gastrointestinal function with emotional changes and with stress has been accepted for centuries on the basis of everyday experience. Abdominal pain, anorexia, nausea, vomiting, weight loss, dysphagia, bloating, gas, aerophagia, regurgitation, heartburn, indigestion, diarrhea, and constipation have all been ascribed to emotional change. Nowhere has this been more extensively studied than in gastroduodenal function and its relationship to peptic ulcer disease.

The psychosomatic theory of peptic ulcer supposes that ulcer patients are exposed to longstanding psychic conflict, anxiety, or tension, resulting in increased gastric acid-pepsin secretion or decreased mucosal resistance, and that an accentuation of these factors leads to the onset of peptic ulcer disease (32). Studies have often attempted to correlate one or more of these factors.

The gastric fistulae of Beaumont's Alexis St. John (33), Carlson's Fred V. (34), and Wolf and Wolff's Tom (35) provided early visual evidence that emotions affect gastric function and led to reports that mucosal hyperemia, increased volume of gastric secretions, and increased acidity were associated with emotional upset, anxiety, hostility and resentment. By contrast, depression and despair led to mucosal pallor and decreased secretion. Hoelzel, studying himself, noted slight increases in gastric acidity in the days surrounding an attempted burglary (36). Although several studies report increases in basal acid secretion in association with stressful interviews or life events, the relationship of these acute events to peptic ulcer is not clear (37–41).

Exacerbations of peptic ulcer have also been associated with stressful life events (42–44). Rose and others reported that air traffic controllers working in high traffic density units followed for three years had a significantly elevated incidence of peptic ulcer (45); however, of the 13 with peptic ulcer symptoms, only 3 had confirmed duodenal ulcers on endoscopy or x-ray, reducing the incidence to control levels (46, 47). Weiner and Mirsky, using psychosocial data, were able to predict susceptibility to peptic ulcer anterospectively (48). Alp et al found a significant increase in domestic and financial stress and consumption of aspirin, alcohol, and cigarettes in patients with gastric ulcer compared with controls (49). Peters and Richardson carefully studied two patients with prolonged severe emotional stress who developed pronounced hyperacidity and gastric ulcers. Both disorders subsided when the stressful problems abated (50). Other studies have found a lack of correlation between ulcers and life events (51).

Some experimental and spontaneous ulcers in animals tend to support stress as a factor in the pathogenesis of peptic ulcer, although often the mechanisms remain unknown. Spontaneous bleeding and perforating ulcers occur in 25%–50% of swine going to slaughter. The "executive" monkey study, an experiment in operant conditioning, demonstrated that the decision-making monkey of the two receiving shocks was the one who was likely to develop the ulcer (52).

A number of difficulties arise in assessing the evidence (32). One is definition. The term peptic ulcer disease encompasses many diseases (53). Another is the problem of assessing emotional states; Margolin, for example, relates the unconscious rather than the conscious emotional content to the psychophysiologic response (54). The widely held belief that ulcers are associated with anxiety may distort results in which life events are reported. Mechanisms remain poorly understood; increased vagal tone and epinephrine-stimulated gastric release have been suggested as possible pathways between stress and acid-pepsin secretion (55). These difficulties in criteria, definitions, methodology, and diagnosis make definitive studies almost impossible. Nonetheless, it seems reasonable that in certain individuals with peptic ulcer disease, stress plays a significant role in pathogenesis.

Stress Ulcers. Stress ulcers, hemorrhagic gastritis, acute erosive gastritis, acute gastric mucosal erosions, acute gastric mucosal injury, stress gastric bleeding, acute gastroduodenal ulcer and stress ulcer syndrome are some of the terms applied to a lesion which is now estimated to occur in 5%–10% of patients admitted to intensive care units (56, 57), in 3.6%–6.2% of unselected autopsies (58, 59), and in 6% of patients hospitalized for ulcer disease (60). It was reported in 3% of 2,997 wounded U.S. Army soldiers, in 0.1%–22% of patients after elective surgery, and in 11.7%–25% of patients admitted to a burn unit (61).

In 1936 Selye reported that, in rats, fasting, injecting certain drugs, surgical trauma, restraint, and exposure to cold were each accompanied by involution of the thymus and enlargement of the adrenal glands, and that "with one exception all the animals kept at a low temperature of +1 to 3°C developed gastric ulcers" (62). He later included this feature in his description of the alarm reaction and diseases of adaptation. In the 1960s and 70s a number of reports on the characteristics of this serious and perplexing condition came from studies of intensive care units, trauma centers, burn centers, and groups of seriously ill patients with sepsis, shock, respiratory or renal insufficiency, postoperative complications, or multiple injuries. In 88 cases at Baylor, mortality was 50%; sepsis, in 57%, caused the highest mortality (76%). Surgery and trauma accounted for 65% of the cases. The authors maintained that a single ulcer, present in two-thirds of the cases, was the usual presentation in stress, and emphasized corticosteroid therapy, stress, and sepsis in pathogenesis (60). In a report of 61 patients with gastrointestinal bleeding who had a history of a stressful physical condition and major bleeding within four weeks of the stressor, the mortality rate was 85% (59). In 1969 Skillman et al reported a fatal syndrome of massive gastrointestinal bleeding in patients with respiratory failure, hypotension, sepsis, and jaundice, in 8 patients of 140 admitted to a respiratory-surgical intensive care unit. The average interval from sepsis or hypotension to bleeding was nine days. Basal acid output after bleeding was 18.3 mEq/hr in burn patients. Seven of the 8 patients died (56). Douglass and Le Veen reported 83 episodes of stress ulcer bleeding in 75 patients; overall mortality was 66%. These authors emphasized the importance of hypersecretion of acid together with mucosal susceptibility induced by stress, or, experimentally, by corticosteroids (63). Patients with a history of peptic ulcer disease constituted 38% of their series. Lucas et al reported 300 cases with 18 deaths, and described serial gastrocamera photographs on 42 of their patients (64). Crawford et al reported on 43 patients at the Duke University Medical Center, along with a series of 162 cases of 4,465 consecutive autopsies. In the clinical series 33% were receiving steroids at the time of bleeding. Sepsis, present in 40%, was associated with a very high fatality rate. The overall mortality was 67%. In the autopsy series, 56% of the cases were undiagnosed during life (58). Stremple et al reviewed 64 cases in 2,997 admissions of American combat soldiers wounded in Vietnam. Of the 33 with proved gastrointestinal lesions, 20 bled from gastric ulcers, 11 from duodenal ulcers, 1 from diffuse hemorrhagic gastritis, and 1 from hemorrhagic necrosis. A few small-bowel and colonic lesions were also found, leading to the designation of the condition as part of a generalized acute gastrointestinal focal necrosis syndrome. Their concept emphasizes the controversy over what constitutes a stress ulcer. Stremple's study included pathologic findings as far away as the colon. Others included esophageal and duodenal lesions; still others regarded multiple gastric erosions, particularly proximal gastric erosions, as the only stress ulcer lesion (61).

The damage to the stomach in these cases is not unlike that produced by certain drugs, by Cushing's ulcer associated with central nervous disease or injury, and by Curling's ulcer, the acute ulcer associated with burns.

Drugs. A number of drugs are capable of damaging the gastric mucosa. The best known of these are the nonsteroidal antiinflammatory drugs and ethanol. The role of corticosteroids is often questioned.

Almost all healthy individuals who take aspirin consistently for a week develop gastric erosions (65). Aspirin damage begins promptly after ingestion and is visible endoscopically within an hour. Erosions and hemorrhage may be seen in the corpus and antrum, less frequently in the duodenum (66). Although single doses of aspirin given intravenously in humans do not produce damage, animal studies suggest that larger doses, particularly in the presence of acid, may (67). Undissociated fat-soluble aspirin in an acid milieu is absorbed into the gastric epithelium; in that more neutral environment, it dissociates into the water-soluble ionized form and is trapped there in high concentrations (68). Aspirin's damaging effects are not well understood, but include (a) reduced mitochondrial oxidative phosphorylation and inhibition of ATP-dependent processes, (b) decreased bicarbonate and normal mucus, (c) inhibition of the biosynthesis of prostaglandins and of prostaglandin cyclooxygenase, (d) direct mucosal toxicity, and (e) breaking the mucosal barrier and its consequences, back diffusion of acid with degranulation of mast cells, release of histamine, microvascular engorgement, inadequate buffering and removal of diffusing acid, mucosal and submucosal edema, inflammation, and hemorrhage (69–71).

Indomethacin has been shown to produce mucosal erosion and gastrointestinal bleeding (71, 72). Damage, not as severe as that caused by aspirin, is dependent on the blood level and independent of means of administration (73). The mechanism resembles, but does not appear to be as acid-dependent, as that of aspirin. This agent breaks the gastric mucosal barrier, reduces gastric blood flow, and does not affect the gastric electrical potential. It inhibits duodenal mucosal bicarbonate (71).

Other nonsteroidal antiinflammatory drugs appear capable of causing mucosal damage, but are less well studied and understood. Most appear to cause less damage than aspirin and indomethacin, possibly related to decreased potency. Carprofen, which does not inhibit prostaglandin synthesis in the gastric mucosa, has no significant adverse effect on its integrity (74).

Ethanol is directly injurious to the gastric mucosa in proportion to its concentration and duration of contact. Gastric concentrations over 14% break the gastric mucosal barrier and lower the electrical potential difference (75–77). Acid and aspirin aggravate the damage (75, 76). The mechanism of damage is not clear. Microscopically, the effects are similar to those of aspirin (71). Lipid solubility may play a role in allowing easy penetration of the mucosa with subsequent damage to the mucosal blood vessels (78). Disturbance of membrane functions and stimulation of acid secretion, largely by nonethanolic ingredients of alcoholic drinks, apparently play a role (79, 80).

The effect of corticosteroids on the gastric mucosa is controversial and appears to be complex. Because of data indicating gastric hypochlorhydria in Addisonian patients and an increase in peptic ulcer disease in those treated with corticosteroids, these compounds were believed to increase gastric acid secretion and to induce ulcers (81–84).

Domschke and associates demonstrated in 1972 that gastric mucosal cyclic AMP is drastically reduced in the rat following adrenalectomy, that reduction is in proportion to the decrease in hydrochloric acid secretion, that the cyclic AMP and acidity are restored by dexamethasone (but not by mineralocorticoids), and that dexamethasone administration to the intact animals does not increase cyclic AMP. This, as the authors stated, suggests a permissive, but not active, role for glucocorticocoids in gastric acid secretion (85).

The prevalence of ulcers in a large group treated with corticosteroid of ACTH was not significantly different from controls. Gastric injury was increased only when the prednisolone was given for more than one month and the dose exceeded 1000 mg (86). Other clinical studies correlating corticosteroids to peptic ulcers have produced varied results. There is, in some, a suggestion that long-term or high-dose glucocorticoids have more adverse effects on the gastroduodenal mucosa than short-term or low-dose use. There is also the possibility that certain subgroups, such as patients with cirrhosis and hypoproteinemia and nephrotic syndrome, may be more susceptible to their effects than others (87–89). Corticosteroids may increase gastric damage induced by aspirin (90) and may slow the healing of preexisting ulcers (91). A corticosteroid injection protected rats against alcohol-induced gastric damage (92).

Mechanisms by which corticosteroids may damage the gastric mucosa include decreased mucus production (93), inhibition of phospholipase A2 and consequent reduction of prostaglandin synthesis (94), and depressed epithelial proliferation (95) and renewal (96).

Cushing's Ulcer. Cushing's ulcer follows intracranial injury or neurosurgery, resulting in a high incidence of upper gastrointestinal hemorrhage (97, 98). The incidence of bleeding is, in general, proportional to the degree of injury, as high as 42% in decerebrate rigidity in one series (98). In an endoscopic study by the same group, 22 of 36 patients endoscoped within a week after head injury had gastric mucosal erosions, and 13 of the 14 others had various lesions (99). Watts and Clark found gastric acidity levels in such patients enormously high, approaching those seen in gastrinomas (100). Stremple found acid and serum levels in CNS trauma cases elevated over those in intraabdominal injury (61). Hypothalmic stimulation experiments, anticholinergic blockade, and other studies suggest that increased intracranial pressure and hypothalamic and vagal stimulation are directly involved (101–104). Decreased blood volume has also been demonstrated (99). However, ulcerations and bleeding have also been reported in spinal cord injuries (105–106). Although evidence is not conclusive, some patients with central nervous system injury or illness may suffer a stress response similar to those with injury elsewhere, some have a tendency to peptic ulceration antedating the condition, and some among these have unusually high levels of gastric acidity.

Burns and Curling's Ulcer. Swan and later Curling described gastroduodenal lesions associated with burns (107, 108). More recent studies indicate an overall incidence of 12%–25% distinctly increasing in proportion to the severity of the burn (109–112). In a recent series from Sweden, an incidence of 5.5% was attributed to routine antacid prophylaxis (113). The overall incidence in children is two to three times that in adults. Acid secretory studies have shown no consistent hyperacidity or hypergastrinemia.

Endoscopically, erythematous macular lesions in an area of a pale mucosa or confluent erythematous areas with mucosal hemorrhagic erosions were seen in patients examined within 72 hr of the burn. Lesions occurred in the stomach, more often in the fundus but also in the antrum and in the duodenal bulb. The earliest ulcer was seen after four days, suggesting that the original intense superficial mucosal injury progressed to ulceration in some patients as their clinical condition evolved (111). These findings are not unlike those seen by Lucas et al in serial endoscopy. Within 24 hr, multiple shallow red-based erosions and petechiae were found in the gastric fundus. The lesions deepened over the next 24 hr, with black bases and raised margins. Some progressed to the rest of the stomach and some lasted for up to three weeks. These observations are consistent with those associated with changes seen in stress ulcers. However, lesions may be seen in the duodenum and esophagus as well as the stomach, may be deep, and have an increased incidence of perforation. These observations raise continued speculation about whether this condition is physiologically identifiable with the classical stress ulcer (114).

Gastric Physiology

The defensive factors in gastric physiology are particularly relevant to the subject of stress because of evidence that one or more such factors may link the stress event pathophysiologically with the stress ulcer syndrome. Gastric acid secretion remains an important issue in this condition because the presence of lumenal acid is essential for the formation of stress ulcers, and the back diffusion of gastric acid may be a key factor in mucosal injury.

Studies of gastric acid secretion have reported low (92, 115), high (116–118), and low and high (119) results, under varying circumstances, at different times in the course of the disease and using different measurements. Because acid secretion studies generally measure lumenal acid, the result is the net between acid secreted and acid back-diffused, which leads to various interpretations of the result. (A low net acid secretion in the early phase of disease may result from mucosal destruction with decreased secretion, or increased back diffusion, or some other factor).

Back diffusion is part of the gastric mucosal barrier concept, introduced by Code and Davenport in the 1960s as a hypothetical barrier to the flow of acid from the gastric lumen to the mucosa (120). Loss of the barrier not only allows lumenal acid to permeate the mucosa, but allows sodium and potassium into the lumen, causes a fall in the electrical potential difference between the lumen and the mucosa, results in an increased flow of fluid, glucose, and protein into the lumen, and produces an increased histamine content in the gastric venous blood. The barrier may be broken in several clinical situations, including hypotension, sepsis, or uremia, following burns, during the course of intracranial disease or injury, and following exposure to certain agents, including aspirin, alcohol, bile salts, and urea.

The site of the proposed barrier remains unclear, but may be the intact monolayer of gastric surface epithelial cells or the apical surfaces of these cells. Alternatively, there may be no barrier, except for a layer of epithelial cells subject to frequent "physiological" disruption, but capable of quite rapid (15–30 min) turnover (121, 122).

This surface layer of cells also secretes mucus and bicarbonate. The mucus forms an unstirred layer, up to 0.5 mm thick, of 5% bicarbonate and 95% water that acts as barrier to the lumenal acid, slowing its diffusion rate to about a fourth the rate in water. While the gastric glands are secreting acid, the surface epithelial cells secrete bicarbonate at about a tenth the rate of acid. The combination of mucus and bicarbonate impedes acid back-diffusion and maintains pH at the epithelial surface at 7 while the lumenal pH is 2. When the lumenal pH is below 2 this mechanism is defeated, exposing the surface cells to possible acidification and mucosal injury (123).

A defensive factor of uncertain significance is the resistance of the gastric epithelium to wetting by lumenal materials. This hydrophobicity may be conferred by phospholipids in the epithelial membrane (124).

The gastric epithelium proliferates rapidly at a rate second only to bone marrow, turning over completely every three days (125). It appears likely that this rapid growth plays a significant role in gastric mucosal defense. Growth hormone and two other peptides are known to promote this rapid proliferation (126). Gastrin is known to have a trophic property independent of its acid-secreting role (127). (Histamine does not promote growth.) Epidermal growth factor, found in saliva and Brunner's glands, has this quality and has been shown to be protective in several ways; for example, it protects cats and rats against aspirin-induced gastric injury (128).

In addition to its rapid turnover rate, the gastric surface epithelium appears to be able to renew its integrity within minutes of exposure to noxious agents. This restitution or reconstruction is accomplished by the migration of viable mucus neck cells upward to replace the sloughed epithelium and reform a complete lining. Remarkably, this process begins minutes after an injury and is complete in some species in 30 min (121, 122). In the frog, epithelial continuity with tight junctions is formed, the mucosal potential difference is restored, and alkalinization of the lumen is reversed, with return of acid secretion in six hours (129). The process does not involve differentiation or replication, which would take days. It does not seem to involve an inflammatory reaction or to require blood circulation. It does appear to require an intact basal lamina. It is inhibited by a pH less than 3 and the absence of calcium, but not by indomethacin. Prostaglandins have no effect in vitro (121, 122, 125).

Beneath the mucosa, the interstitial fluid bicarbonate has a buffering effect available to neutralize any acid which passes through the epithelium. The source of this bicarbonate is believed to be the alkaline tide, its liberation occurring as acid is secreted into the lumen. Considering this, an actively secreting mucosa would appear to be better protected than one in which acid secretion is suppressed. This could account for the reported superiority of antacids over H2 histamine antagonists in the management of stress ulcers (130). An actively secreting mucosa also has an increased blood flow. Systemic acid-base balance is also a factor in the development of mucosal injury. Systemic acidosis aggravates and intravenous bicarbonate reverses the aggravation. Ulceration induced by hemorrhagic shock in dogs can be prevented by bicarbonate-induced metabolic alkalosis; induced respiratory alkalosis and THAM, a poorly diffusable alkali, were ineffective (131). In the studies by Fidden-Green and associates on pH on patients in intensive care unit, only those whose calculated gastric intramucosal pH fell below control levels had bleeding from stress ulcers (132).

Reduction in gastric mucosal blood flow with its associated energy deficit impairs mucosal ability to neutralize back-diffused acid. This impairment is considered a central factor in the formation of stress ulcers and is present in most models of the disorder (131, 133–139). Kitagawa found no mucosal blood flow changes in a rat model (140).

Prostaglandins and Cytoprotection. Prostaglandins, twenty carbon unsaturated fatty acids with a cyclopentane ring and two aliphatic side chains, have been found in humans as well as other species. Production capacity in gastric mucosal homogenates is considerable, mainly PGE2 and PGF2. The rate of production in humans appears to be under circadian and cholinergic influences. Vagal stimulation results in increased levels in the tissues and gastric lumen. Regulation by neurotransmitters and hormones is largely unknown. Both altered circadian and low levels were found in duodenal ulcer patients, and high and low levels in gastric ulcer (141). Perturbation of cell membranes by a variety of agents is a major stimulus to synthesis. Measurements have been difficult (142).

Cytoprotection appears to play a critical role in gastric mucosal defence (142–144). Administration of prostaglandins and analogs stimulates gastric mucosal blood flow, mucus and bicarbonate secretion, adenylate cyclase activity, and mucosal hyperplasia, decreases hydrogen ion permeability, and in large doses decreases hydrogen ion secretion. Adaptive cytoprotection, in which mild and even unrelated stressors protect the stomach against severe insults, may be a valuable key to the understanding of the relationship of stress to gastric mucosal injury (145–150).

Irritable Bowel Syndrome

Irritable bowel syndrome is a disorder of intestinal motility for which no anatomic cause can be found. Three patterns of altered motility are recognized: spastic colon, painless diarrhea, and diarrhea and constipation. All may be associated with nonspecific complaints, including bloating, gassiness, and nausea and vomiting. Neuromuscular and hormonal abnormalities have been described, but their etiology and their relationship to the underlying basis of the syndrome is unknown. The syndrome may consist of several entities currently not distinguishable.

The association of the condition with emotional changes has been attractive but controversial. Painless diarrhea, in particular, may be attributed to a stressful event. Although the data (151–154) suggest that patients with irritable bowel syndrome are a psychologically abnormal population, the limitations of psychometric assessments and psychosomatic research (155) make firm conclusions difficult. Patients with symptoms will often appear more neurotic when the measurements are not standardized to a medically comparable group. It is also not clear whether the observations apply to a population with the irritable bowel syndrome, or to that portion of them seeking health care.

Inflammatory Bowel Disease

Almy (156), Engel (157), and others recognized certain personality characteristics in up to 75% of adult patients with ulcerative colitis. These included timidity, lack of emotional depth, reluctance to act aggressively or to satisfy sexual and other instinctive drives, subnormal capacity to develop a warm friendship with a parent or parent surrogate, depression, despair, helplessness, and guilt. Exacerbations may be the result of any one of many real, threatened, or fantasied interruptions of a key relationship.

Methods of investigation include assessment of personality and personal characteristics, correlations by interview or questionnaire between events and illness, observation of patients, and projective tests. The ability of these methods to establish an etiologic relationship remains in doubt. Major personality disturbances are found in as many as 30% of an unselected urban population. Selection of an appropriate control group remains difficult. Observational evidence may be questioned on the basis of the reliability of the diagnosis. *Campylobacter,* ischemic disease, and other colitides may be confused with one or another form of inflammatory bowel disease. Crohn's disease of the colon has been clearly differentiated from ulcerative colitis only in the past two decades, and the two are still occasionally confused. Separating the somatopsychic effects of the illness itself as a stressor from the psychosomatic effects is a challenge.

Engel regarded the mechanism by which ulcerative colitis is precipitated as speculative (152). Several studies have failed to find significant personality abnormalities or precipitating stressful events in ulcerative colitis patients (154, 158–160).

Helzer and associates found a greater rate of psychiatric diagnoses in Crohn's disease patients, notably depression, than in a control group (161). But Feldman and associates found no such evidence in their controlled study (162).

It remains unclear whether psychological factors, particularly stress, can induce and sustain damage to the intestine resulting in inflammatory bowel disease. Whether exacerbations or variations in symptoms may be stress related seems far more tenable, but remains to be proven.

Summary

The association of several gastrointestinal diseases with stress is based largely on correlation and inferential information. Limitations in the definition of stress as well as in the taxonomy of gastrointestinal disorders represent initial barriers to clearcut data. The frequently subjective nature of the material and the seeming pervasive nature of stress add to the difficulty. These factors apply to esophageal disease, peptic ulcer disease, the irritable bowel syndrome and inflammatory bowel disease.

The stress ulcer syndrome, however, is an attractive candidate for a truly stress-induced disease. Experimentally and classically it occurs in a wide variety of trying situations. In many, the implication is that the adaptation to challenge elsewhere in the body is met by depriving and perhaps eventually sacrificing the gastric mucosa. Deprivation is experienced elsewhere, physiologically, for example, in the distribution of arterial circulation as a response to metabolic requirements. The pathophysiology of the events leading to the sacrifice in the stress ulcer syndrome, with ulceration, gastrointestinal bleeding, and possibly death, is an important key to the understanding of how stress can lead to disease. We need to know whether the primary failure is in the circulatory changes, local or systemic acidity, energy, prostaglandin synthesis, or elsewhere to better understand the limits of adaptation. The final common pathway may be the failure of the gastric mucosa to cope with the lumenal acid with which it is presented. But the gastric mucosal blood flow, prostaglandin synthesis, acid-base factors, and other factors bear on this, and in some instances can be manipulated to effectively prevent the condition. The fact that they fail means that the stress ulcer syndrome is not an extreme of adaptation, but rather a disease of stress failure.

Despite the inconclusive evidence in much of the literature relating stress to the etiology of gastrointestinal disorders, clinicians as well as researchers pay considerable attention to stress in their management of these disorders. Common sense as well as biochemistry and physiology continue to identify stress as a significant aspect in the care of individuals with gastrointestinal disorders, as amply demonstrated by Beaumont, Cannon, Almy, and their descendants.

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Stress and Visual Function

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Abstract

Stress may contribute to various ophthalmologic disorders. Many ophthalmologic conditions usually considered purely physical or organic may be shown to be significantly influenced by emotional factors. The relationship between stress and essential blepharospasm, multiple sclerosis, thyroid ophthalmopathy, uveitis, and glaucoma is discussed. In addition, suggestions for rehabilitating the visually impaired individual are briefly outlined.

Stress may contribute to various ophthalmologic disorders. Considering the multitude of psychosomatic reactions involving the cardiovascular system, the gastrointestinal tract, the endocrine system, the respiratory tract, and the skin, it would not be presumptuous to include the eyes as organs affected by psychopathologic events. In ophthalmology, many conditions considered purely physical or organic may be shown to be significantly influenced by emotional factors. Thus, one cannot exactly delineate between "psychosomatic" and purely "organic" conditions. Moreover, many patients have an emotional reaction to their illness or a psychogenic overlay to their organic problem. Certain ophthalmologic conditions related to stress, including essential blepharospasm, multiple sclerosis, thyroid ophthalmopathy, uveitis, and glaucoma, are discussed.

Essential Blepharospasm

Essential blepharospasm is a chronic, variably progressive disorder in which bilateral, usually symmetrical, lid closure occurs. It may be severe enough to cause a significant visual handicap despite normal neural pathways for vision. The emotional and economic crippling associated with this disorder usually lead these patients to seek an ophthalmologic evaluation first, either because of external irritation or because of visual impairment resulting from the frequency of the blepharospastic episodes.

Most neurologists consider essential blepharospasm to be a focal dystonia of organic origin (1, 2). Other physicians who treat the condition maintain a belief in a predominantly psychogenic cause (3). All physicians treating such patients acknowledge that, on occasion, it can be mimicked by psychogenic blinking (4). Features that might suggest a psychogenic cause include the fact that the movements (a) can be duplicated voluntarily, (b) follow an unpredictable course, worsening under stress or observation, (c) are usually not associated with structural lesions on computed tomography or at autopsy, (d) may appear to be precipitated by an emotional crisis, and (e) are often ameliorated by certain "trick" maneuvers the patient has discovered.

Essential blepharospasm has also been attributed to an organic cause, justified chiefly by the occasional appearance of identical symptoms with idiopathic Parkinsonism (5), postencephalitic Parkinsonism (6, 7), and other basal ganglia diseases (8). Spontaneous blepharospasm following focal central nervous system lesions is rare, but six such patients were reported who had associated rostral brainstem damage (9). In a recent report (10), delayed onset of continual blepharospasm followed severe cerebral hypoxia that

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reduced the patient's useful vision. Additional basal ganglia signs included postural defects and rigidity, as well as severe dystonic posturing of the hands. Symmetric basal ganglia infarcts were demonstrated with computed tomographic scanning. Similar basal ganglia infarcts have been reported with hypoxic encephalopathy after carbon monoxide poisoning (11), near-drowning (12), and strangulation (13).

Essential blepharospasm and blepharospasm associated with orofacial dystonia (Meige syndrome), like torsion dystonia, are not associated with structural central nervous system pathology (14). Three of Jankovic and Patel's (9) 6 patients with symptomatic blepharospasm manifested computed tomographic evidence of thalamic-upper midbrain infarcts, and all displayed symptoms pointing to this anatomic area. Their patients developed blepharospasm after delays ranging from two days to three years following infarction (4 patients) and involvement by multiple sclerosis (2 patients). Based on these data, it is reasonable to consider that essential blepharospasm can be induced by either psychogenic or organic changes.

The present treatment of blepharospasm is somewhat unsatisfactory. No drug provides predictable long-lasting relief. Surgical therapy has been used to alleviate orbicularis spasm via selective facial nerve denervation or by directly cutting the muscle (15). The use of botulinum toxin to weaken the orbicularis muscle has been recently described (16). Psychogenic blepharospasm is more amenable to treatment.

Multiple Sclerosis

Multiple sclerosis is a leading cause of serious neurologic disability among young and middle-aged adults in the United States. Signs commonly appear in a patient's most promising and productive years, the thirties or earlier; women are affected more often than men. The annual economic impact of multiple sclerosis is estimated to be $1.7 billion. In addition to the neurologic disorder, economic loss is the overwhelming emotional burden that multiple sclerosis imposes on the patient and family.

A survey by the National Institute of Neurologic and Communicative Disorders and Stroke in 1976 revealed that in the United States about 123,000 people suffer from multiple sclerosis, with 8,000 new cases diagnosed annually (17). The prevalence rate on January 1, 1976 was 58 cases per 100,000 people. The incidence rate was 4 per 100,000 people. The average survival time is 30 years from onset.

Multiple sclerosis is a chronic disease of the central nervous system that hinders the ability of the brain and spinal cord to process motor, sensory, and visual impulses. The patient's most basic functions are seriously impaired; symptoms include loss of vision, difficulty in walking, impaired bladder control, tremor, and problems with speech. The characteristic feature is the destruction of myelin, the fatty substance that ensheathes nerve fibers in the brain and spinal cord. As the myelin is destroyed, scar tissue, called plaques, is produced where the myelin is lost. Thus, the transmission of messages directed to and away from the brain and spinal cord is inhibited or completely obstructed. This produces the well-known symptoms and signs.

The cause of the destruction of myelin is still a mystery. Many scientists suspect that the immune system is overactive in the disorder, which appears when the body directs its defensive attack against itself. The role of viruses in chronic neurologic disorders such as multiple sclerosis is still unclear.

The course of the disease generally follows either a relapsing-remitting or a chronic progressive pattern. A few patients may experience only one episode. In the National Survey, the first study to provide scientifically reliable national statistics for multiple sclerosis, 70% reported a relapsing-remitting pattern and about 30% a chronic progressive course. The symptoms reported varied, depending on which part of the nervous system was damaged. Nearly every patient experienced weakness, numbness, nystagmus, difficulty with coordination, and loss of balance. Two-thirds also experienced loss of bowel or bladder control. Patients reporting incontinence had multiple sclerosis longer than those who did not. Disturbances of vision affected about 70%. Other symptoms included speech problems (about 50%), and dizziness (about 45%). In general, visual disturbances, speech problems, and dizziness were experienced by people whose disease commenced before 40 years of age.

Multiple sclerosis has long been associated with a variety of functional disorders. In 1874, Jean Marie Charcot first observed that the intellectual and emotional faculties of patients with multiple sclerosis are "blunted in their totality" (18). Several studies examining the nature and prevalence of emotional disturbance in multiple sclerosis patients were undertaken in the 1920s. Brown and Davis (19) reported "mental alterations" in 90% of cases and considered euphoria to be present in 71% of 14 patients examined. Sachs and Friedman (20), in a retrospective review of 146 hospital cases, reported explosive laughter and emotional instability in 17% and mental change in 16% of patients. Cottrell and Wilson (21) examined 100 consecutive clinic patients and concluded that "the cardinal symptoms of multiple sclerosis belong to the emotional, affective, and visceral spheres, and are constituted by changes in mood, bodily feeling, and in emotional expression and control." They reported the prevalence of euphoria as 63%, depression 10%, labile mood 23%, and indifference 2%. Wechsler (22), on the other hand, noted the presence of impulsive laughter, euphoria, and nervousness in only 9% and irritability, depression, and memory deficit in 12% of 1,773 multiple sclerosis patients.

In 1969, Surridge (23) undertook the first controlled study of psychiatric changes. Based on direct clinical observations, he found depression in 27% (29) of 108 multiple sclerosis patients as opposed to 13% (5) of 39 muscular dystrophy control patients. Euphoria, seen in 26% (28) of multiple sclerosis patients, was strongly correlated with intellectual deterioration and was not observed in the control patients.

In 1983 a study (24), reported the results of observations of emotional disturbance in patients with multiple sclerosis who were followed monthly in a controlled study for one year with self-administered questionnaires. The prevalence and degree of emotional disturbance in patients in remission during the study period was compared with that of patients with active demyelinating disease and spinal-cord-injured controls. The study revealed that significant and potentially severe emotional disturbance was associated with increasing disease activity in patients with multiple sclerosis. Less emotional disturbance was observed in spinal-cord-injured controls who were more functionally disabled than their multiple sclerosis counterparts, suggesting that emotional disturbance in multiple sclerosis is not just a reaction to sensorimotor deficits. Moreover, the finding of markedly abnormal general health questionnaire scores in many multiple sclerosis patients during exacerbation contrasted with the slight elevation in mean general health questionnaire scores in multiple sclerosis patients in remission compared with spinal-cord-injured controls, and implicated disease activity or exacerbation as an important precipitant of emotional disturbances. The prevalence of emotional disturbance was 90% in exacerbating or progressing patients, 39% in stable patients, and 12% in spinal-cord-injured control patients.

Alternate hypotheses explaining the higher prevalence of emotional disorder in multiple sclerosis patients include (a) the unpredictable and uncertain course of the disease, (b) plaques occurring in brain areas associated with mood, affect, and cognition, and (c) demographic differences between multiple sclerosis and control patients. One previous study (25) noted more depression in exacerbating than in remitting multiple sclerosis patients.

It cannot be determined whether increasing emotional disturbance precedes, is concomitant with, or follows exacerbations (26). Increased sensitivity to and prompt recognition of changes in emotional state accompanying exacerbation might relieve or lessen emotional distress, aid in adjustment to new deficits, and improve cooperation with therapy. It is also known that fright, anger and excitement, anxiety related to familial problems, and intercurrent illness may produce exacerbations of the disease.

Although there is no proof that emotional factors play a role in the etiology of multiple sclerosis, there is ample evidence that the symptoms may become exaggerated by stressful situations. Moreover, being told the diagnosis is in itself a stressful situation. The course of the disease and the patient's reaction to stress are different. A patient is likely to experience certain psychological stages in varying order, including denial ("It's not happening to me"), resistance ("It won't get me down"), affirmation ("I guess I'll have to face it"), and integration (living with it).

Thyroid Disorders

Stress of any sort may precipitate thyroid dysfunction. Hyperthyroidism may appear at any time from childhood to old age. The most common cause of both bilateral and unilateral exophthalmos is the orbitopathy of Graves' disease. Normal thyroid function does not eliminate the existence of Graves' orbitopathy because the ocular signs may occur in the absence of thyroid disease, an entity known as ophthalmic Graves' disease.

The ocular findings of thyroid dysfunction are classically described as toxic and congestive. The principal toxic manifestation is retraction of the upper eyelid, or stare, which exaggerates the appearance of exophthalmos. Lid retraction may be reversible when the underlying hyperthyroidism is treated. Congestive signs are the result of lymphocytic infiltration and enlargement of orbital tissues by inflammatory edema, followed by fibrosis. The major congestive signs of Graves' disease are exophthalmos, periorbital edema, and limitation of eye movements.

Restricted eye movement produced by pathologic changes in extraocular muscles secondary to thyroid dysfunction is a common cause of diplopia. Dysthyroid restrictive myopathy is the most common cause of spontaneous double vision in middle age and early senescence. Moreover, thyroid myopathy is commonly missed. In subtle cases, the striking clinical signs of congestive proptosis are absent, but spontaneous lid retraction or lag on gaze downward can be observed. As the eyes turn downward, one or both lids are noted to lag or "hang up." At times, a peculiar edema is often evident in the upper or lower eyelids, but this may be difficult to distinguish from the redundancy of eyelid tissue that accompanies aging. The conjunctival vessels overlying the anterior aspects of the horizontal recti muscles are usually dilated and tortuous. In fact, hypertrophic extraocular muscles may be visible. The most common ocular motility pattern encountered is unilateral elevator palsy, which increases on gaze upward. This is secondary to fibrotic shortening of the inferior rectus muscle, which restricts upward rotations. Similar fibrotic contraction of the medial rectus muscle produces a defect in abduction which may mimic a sixth-nerve palsy, but the globe resists outward rotation when the insertion of the medial rectus is grasped. Downward gaze may be limited when restrictive fibrosis of the superior rectus muscle occurs. Combinations of restrictive muscles may result in bizarre motility patterns. An additional clue is the finding of elevation of intraocular pressure on attempted upward gaze, which is attributed to a fibrotic and taut inferior rectus muscle.

Graves' orbitopathy threatens vision in two ways, by exposure and by optic neuropathy. Exophthalmos and lid retraction may combine to expose the cornea to drying, and in extreme cases, infection, perforation, and loss of the eye may result. The enlarged muscle mass in the orbital apex may compress the optic nerve and can thereby reduce vision.

The ocular manifestations may antedate laboratory or clinical evidence of thyroid dysfunction, but many patients have ophthalmologic complications months to years after surgery or radioactive iodine therapy for hyperthyroidism. At the time of diagnosis, many of these patients may be biochemically euthyroid. Through corticothalamic pathways, psychological processes can exert their influence on the hypothalamus and thus on the pituitary gland and through it on any remaining thyroid tissue.

Uveitis

The iris, ciliary body, and choroid together form the uveal tract. Inflammation of the tract is called uveitis. Patients suffering from anterior uveitis, also known as iritis or iridocyclitis, often have a red eye associated with aching pain but no discharge. Photophobia and tearing may be prominent. In mild iritis, there may be a perilimbal injection in a pattern known as ciliary flush, but with more severe iritis, the injection is generalized. The anterior chamber cellular reaction is the hallmark of anterior uveitis, consisting of keratitic precipitates on the corneal endothelium. These usually resolve as the inflammation diminishes but may persist after the anterior chamber reaction has terminated. However, the inflammation may produce binding of the iris to the lens, posterior synechiae, or to the cornea, peripheral anterior synechiae.

Iritis initiated by trauma or surgery tends to be self-limited. Iritis may also be a feature of some infectious and systemic diseases, including sarcoidosis, toxoplasmosis, tuberculosis, collagen vascular disease, and syphilis. Most spontaneous iritis, however, is idiopathic. With posterior uveitis, there is inflammation of the choroid extending to the retina. There may be exudates involving the choroid and retina associated with edema and hemorrhages. Inflammation of the optic nerve and vitreous can also be associated. Inflammation of the entire uveal tract is referred to as panuveitis. Both anterior and posterior uveitis can produce impairment of vision.

The etiology and pathogenesis of endogenous uveitis are uncertain. As early as 1854, Mackenzie (27) stated that emotional factors are important in the etiology of uveitis. In cases of recurrence not responding well to cycloplegic and topical steroid therapy, an attempt should be made to determine whether any stress factor is operative, so that the patient can be treated as a whole (28). How stress acts as a precipitating factor in an attack of uveitis is not clear. Local somatic as well as chronic or acute emotional trauma may be the exciting factor in herpes zoster ophthalmicus (29). The role of stress in uveitis was evaluated in 40 patients by Kumar, Nema, and Thakor (30). Neurohumoral and endocrine studies were performed to assess biochemical changes in stressful situations. Mean plasma epinephrine, norepinephrine, and cortisol levels were statistically significantly elevated in patients suffering from recurrent uveitis. The biochemical changes in uveitis may be attributed to stress working through the pituitary-adrenal axis, probably creating a relatively ischemic state in the uveal tract, depleting local body defense mechanisms.

The most distressing aspect of uveitis is its tendency to recur, in certain individuals as often as 5–10 episodes per year. The decreased cellular immunity seen among the elderly may play a role in recurrence of some forms, particularly in ocular toxoplasmosis and herpes zoster, in which exacerbations of inflammation may occur within a few weeks after the apparent healing of a lesion. Phair and associates (31) have documented reduced T-lymphocyte cellular reactivity among the aged, findings confirmed by Antel and coworkers (32). In addition to diminished T-cell responses to specific antigens, reflected in the decreased uptake of radioactive thymidine by their antigen-stimulated lymphocytes in tissue culture, the elderly show other signs of diminished cellular reactivity, including cutaneous anergy to intradermally injected antigens. Thus, they may be considered immunologically compromised hosts.

Many investigators interested in the recurrence of uveitis believe that emotional stress is a precipitating factor in the recurrence of some forms. Recurrence has been seen among individuals who had recently lost spouses or among patients physically and emotionally exhausted from prolonged death-bed vigils. Divorces, business losses, failure to pass examinations, and other similar forms of emotional trauma, particularly if accompanied by a lack of sleep or other forms of physical exhaustion, have often been followed by exacerbations (33).

Until recently, it has not been possible to analyze the pathways by which emotional stress could produce such recurrences. Work of the last decade has indicated definite neurophysiologic connections, not only with hormone release systems but with the immunological defense system as well. Neurotransmitters of the autonomic nervous system play a role in the various activities of lymphocytes and in the activities of certain organs that process lymphocytes, notably the thymus and the spleen. This may provide the essential key to the process by which emotional stress of cerebral origin is translated into immunologic events, which, in turn, are reflected by inflammatory changes in the target tissues. Hadden, Hadden, and Middleton (34) demonstrated adrenergic receptors on human peripheral lymphocytes in 1970. They were able to show that α-receptor stimulation by norepinephrine resulted in augmentation of phytohemagglutinin-stimulated uptake of tritiated thymidine. On the other hand, β-receptor stimulation by isoproterenol resulted in an inhibition of thymidine uptake in the early stages of incubation and an augmentation in the later stages. These findings must be contrasted with those of Besedovsky and associates (35), who found that norepinephrine and the α-adrenergic agonist clonidine suppressed immune responses in vitro. It is most likely that suppression of T-cell-mediated responses is crucial to the emergence of opportunistic pathogens such as *Toxoplasma* and herpes under stress-related conditions.

The thymus and the spleen are also innervated by terminals of both the adrenergic and cholinergic nervous systems. These organs are innervated by branches of the cervicothoracic sympathetic nerve trunk and the vagus, respectively. These organs may have direct connections with the central nervous system. Direct neuronal connections between the nucleus ambiguus of the brain stem and the thymus gland of both rats and mice have been demonstrated (36). Similar connections may eventually be shown in humans.

Glaucoma

Glaucoma is characterized by elevation of intraocular pressure sufficient to cause either temporary or permanent impairment of vision. The increased intraocular pressure damages the optic nerve and reduces visual-field function. The level of pressure in the eye at any given time represents primarily a balance between the rate of formation of aqueous humor and the amount of resistance to its flow out of the anterior chamber.

On the basis of gonioscopic evaluation, two clinical types of primary glaucoma may occur in the adult: chronic simple (open, wide-angle) glaucoma, and narrow-angle (angle-closure, acute congestive) glaucoma. Chronic simple glaucoma is characterized by an open filtration angle and a chronic, insidious course. It occurs more frequently than acute glaucoma, and its incidence increases significantly with age, affecting an estimated 2% of the population over 40 years of age. In narrow-angle glaucoma, there is a very narrow or closed angle resulting in episodes of elevated intraocular pressure associated with acute congestion, pain, and blurred vision. Angle-closure glaucoma may not be painful, especially in elderly people. The only clues may be an unreactive pupil and decreased visual acuity. Some patients never have an acute episode and present as if they are suffering from chronic open-angle glaucoma.

Acute angle-closure glaucoma is a multifactorial disease for which the risk factors include genetic predisposition, female gender, shallow anterior chamber depth, increased lens thickness, smaller corneal diameters, and increasing age. In aging patients, growth of the lens tends to gradually increase resistance to the flow of aqueous forward through the pupil. Although precipitating events in individuals at risk are poorly understood, emotional factors may be causative (37).

Inman (38) first postulated that emotional upsets could precipitate acute angle-closure glaucoma. Ripley (39), a psychiatrist, kept a record of intraocular pressures in a patient during various emotional states and reported fluctuations in intraocular pressure with changes in mood. Croll and Croll (40) supported these concepts and reported 3 patients who developed “emotional glaucoma”; 2 of them immediately after surgery. Egan (41) reported 4 patients who developed angle-closure glaucoma after a fall and coined the term “shock glaucoma.”

In some cases of angle-closure glaucoma, an attack may be precipitated by strong emotion. An acute attack can be evoked by dilation of the pupil and theoretically by congestion or increase in volume of the intraocular vascular bed. This type of glaucoma has developed acutely in an anatomically predisposed eye when the patient has been subjected to strong emotional upset, such as the death of a close relative or a severe physical injury or illness. Dilation of the pupil and congestion of the intraocular vessels may be associated with grief and crying or with intense anger. In addition, psychological stress in the surgical patient may increase the risk of this disease by causing pupillary mydriasis (37).

Coping with Blindness and Relieving Stress

Emotional stress is known to accompany visual problems. Loss or threatened loss of visual function is inevitably accompanied by serious emotional stress which may not always be immediately evident. The way in which a patient handles this stress can benefit or hinder his or her physical and mental health. Patients usually respond to loss of vision in one of three ways: by acceptance, by denial, or by depression—with or without concomitant anxiety. The response of a given patient can usually be predicted by the patient’s previous responses to emotional stresses (42). Acceptance and denial are the two most frequently encountered patterns. Depression, although the least common response to partial visual loss, may be lethal.

The principal causes of blindness in the aging population of the United States include macular degeneration, cataract, glaucoma, and diabetic retinopathy (43). Dr. DeWitt Stetten, Jr., who suffers from macular degeneration, reemphasized the importance of the physician’s ability to help his patient cope with blindness (44). His very personal discussion was apparently provoked by Dr. Stetten’s inability to obtain advice regarding devices and programs that can improve the lives of blind people.

In the United States, legal blindness is defined as vision of 20/200 or less in the better eye with correction, or a visual field limited to 20° or less in the greatest diameter, even though central vision may be 20/20. Many legally blind people have never been told of training programs that can help them maintain or restore their independence and mobility, or of several instruments that can keep them in touch with the printed word. Visual loss that is not preventable does not have to end the productive life of an individual or force a withdrawal into a narrow world. Ophthalmologists and/or optometrists should perform an evaluation for low-vision aids, basically an extension of a refraction in which an individual may be fitted for specialized eyeglasses in order to make use of whatever vision is left.

Many government, voluntary, and self-help organizations throughout the country provide free or low-cost training and equipment to the blind. In New York State, the Commission for the Blind and Visually Handicapped should be consulted by legally blind individuals. This agency can inform the patients of useful opportunities and information. The American Foundation for the Blind publishes a *Directory of Agencies Serving the Visually Handicapped in the United States* available in many libraries.

Dr. Stetten describes some of the devices that helped him. Visualtek, a televisionlike machine, greatly magnifies printed or written material. The free Talking Books Program conducted by the Library of Congress and Recorded Periodicals can help one keep up with world literature and scientific developments. Other devices mentioned by Dr. Stetten include a braille watch and a talking clock (pushing a button makes a voice announce the time). The Kurzweil reading machine scans printed or typewritten pages and reads them aloud. There are also machines that translate printed words into braille; braille typewriters; Opticon, which translates what it sees into an image that can be felt; telescopic goggles; and Sonicguide, a tiny navigational device. Large-print books and journals and a large-print edition of the *New York Times* are available.

Other useful information for improving the quality of life for visually impaired people was described by Janet E. Brody in the *New York Times* (45), including American Foundation for the Blind publications: a descriptive pamphlet called *Aids for the Eighties;* an order guide, "Products for People with Vision Problems"; and its *Catalogue of Publications* listing printed materials pertinent to people with low vision.

The Vision Foundation was developed by people who were losing their sight, in order to address needs not being met by professionals in the field. It has published, both in large print and on cassette tapes, a handbook called *Coping with Sight Loss* giving a wide range of information about resources such as aids and devices, low-vision and mobility services, recreation, tax benefits, reading materials in special media, and local and national referral sources.

As Dr. DeWitt Stetten asserted, "Decreasing visual acuity need not mean total dissociation from the real world." It is incumbent on all physicians and health care personnel to direct patients with visual impairment to one or more of the aids and agencies designed to improve their quality of life.

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Social Work Management of the Alzheimer's Patient: Who Needs the Support?

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Abstract

Care for the Alzheimer's disease patient is available from family members, geriatric day care programs, and institutions. Support for caregivers is crucial to help with this difficult task. Social work management provides support by helping family and staff learn to respond to the patient, not to the patient's behavior, counseling family members and teaching all caregivers to ask the question, "Does it really matter if it's Tuesday?" (in whose world of reality are we asking the patient to function?). Staff and families learn from each other interventions that are helpful in caring for patients. Day care offers temporary respite for families. When they can no longer tolerate the pressure of care, institutionalization provides immediate physical and emotional relief but creates other stresses. Individual counseling of family members is often indicated to work through emotions of remorse, ambivalence, and mourning.

> The second book of Samuel (II Samuel 6:6) tells how the Holy Ark, which earlier had been captured by the Philistines, returned to the Israelites. The oxen drawing the wagon carrying the Ark stumbled. Uzzah, fearful for the Ark, grasped it in an attempt to prevent the Ark from toppling: thereupon he was stricken dead. A Rabbi was asked why Uzzah deserved such punishment. Interpreting the event, the Rabbi reasoned with a striking observation. The oxen had slipped and stumbled, therefore they needed the help. Why not try to steady the oxen, since the trouble was with them and not with the Holy Ark? (1).

Alzheimer's disease is being researched and studied on the most sophisticated levels known to modern medicine, from genetic and immunologic defects to transmission by a slow-growing virus (2). To the extent that treatment and care are available for the Alzheimer's patient, the "Ark" is being prevented from toppling. How do we steady the "oxen"—the family members, the professionals and nonprofessionals giving the direct care? Although training and support are available to the staffs of institutions and some community programs, the family members are stumbling alone most of the time with the difficult and often lonely task of pulling the Ark.

This paper addresses social work management in three areas of intervention: (a) helping family and staff learn to respond to the patient, not to the behavior; (b) counseling family members; (c) teaching all caregivers to ask the question, "Does it really matter if it's Tuesday?"

Social work intervention may begin with counseling a daughter who has threatened the staff not to overmedicate her father; calming an angry husband who believes his 75-year-old wife's dementia was caused by a prolonged overdose of psychotropic drugs; helping a wife who brought her 63-year-old ambulatory husband to the institution and pleaded for immediate admission; listening to a son who tearfully relates that the only help a psychiatrist gave his mother was to increase or reduce her medication; assisting a frantic woman who requested that Day Care accept her aunt that very day because the exasperated homemaker had quit.

Observations, case histories, and interven-

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tions in this paper are based on experiences at the Kingsbridge Center of The Jewish Home and Hospital for Aged (JHHA) in the Bronx. A teaching affiliate of The Mount Sinai Medical Center in New York City, JHHA is a voluntary geriatric center that provides five levels of care to over 2000 elderly. In 1985 over half of all applications received for the Geriatric Day Care program and for the inpatient beds at Kingsbridge Center were for patients with some form of dementia.

An Irrational Disease. Most diseases progress logically. Alzheimer's disease does not. Given a series of medical treatments, most patients' symptoms and behavior are predictable. Alzheimer's is an irrational disease, whose victims confuse those around them: "Sometimes they act as they always have but at other times become unfamiliar, unreachable, and untreatable" (3).

The irrationality of the course of the disease and the patient's unpredictability result in family and professional caregivers being angry at each other: "Why can't you help me?" "There is little more that we can do." In recent years, no other chronic disease confronting the middle-aged and older populations has presented such a challenge for caregivers to band together. All caregivers—in the community, in day care centers, and in institutions—must share what they learn and support each other in managing the Alzheimer's patient.

Patients with this irrational disease frustrate the doctor who wants Mr. J., a 63-year-old wanderer, to sit with his feet elevated to reduce his edematous ankles, the nurse whose routines are turned topsy-turvy by Mrs. K.'s continual disappearing, and the social worker who is asked to open and close an application within the same week because the applicant has improved.

Responding, not Reacting. What do the family members have in common with physicians, social workers, nurses, and recreation workers who provide the professional care in the institutions and the community? A sense of helplessness couched in frustration because there is no effective treatment, management is stressful, and as one tearful wife stated, "I don't know if Carl even understands that I am trying to care for him."

Helping the distraught spouse, the overburdened nurse, the impatient doctor, the overwhelmed aide respond, not react, to the Alzheimer's patient can interrupt that momentary frustration which makes a professional feel helpless and a family member guilty. Mastering the fine-tuning between responding to the patient rather than reacting to his behavior permits the caregiver a few precious seconds to ask, "What does the patient want? Is the patient in pain? Am I reacting to my own fear of the patient or frustration in not knowing what to do? Am I exhausted? Will what I do make any difference?"

Case History. A 75-year-old man is ambulatory and living with his wife in the community. His diagnosis is Severe Cognitive Decline with Middle Dementia (4). He often failed to recognize his wife, on whom he was entirely dependent for survival. She could cope with embarrassing, inappropriate behavior so long as he acknowledged her as his wife.

A panic call for placement came after a volatile outburst: he had ragingly demanded that she get out of the apartment and send in his wife. Unsuccessfully repeating that she was his wife, she felt herself losing control.

Following a comprehensive interview, the social worker assessed that she was not ready to institutionalize her husband. She accepted a plan for him to enter JHHA's Geriatric Day Care program while she had weekly social work counseling sessions. Counseling began with role-playing to help her understand her husband's irrationality and that his denying her as his wife would continue. How could she respond rather than react to the behavior that distressed her?

In responding to "I want my wife," which may be a momentary, symbolic cry for help, she could suggest calmly, "Let's have a cup of coffee," or "Let's watch TV," or whatever had meaning in their past relationship. When safety is not a factor and an attendant is available, responding could mean leaving the room. Expressing her own frustrations by screaming, crying, or wishing him dead is best done in the privacy of another room. Reacting in front of the Alzheimer's patient leaves the family member feeling ashamed and helpless.

The literature identifies the burdens that characterize the lives of the family members caring for the Alzheimer's patient (5). "Family burden" is broadly defined as disruption of the caregivers' day-to-day lives, embarrassment over deviant behavior, and general overload (6). Other areas of stress include an inability to obtain community services, a lack of support from friends and relatives, and financial difficulties.

Geriatric Day Care

When the burden becomes overwhelming, the family shifts some of the care to a home attendant, seeks placement in a day care program, or considers institutionalization. These new caregivers take up the task of pulling the "Ark" and need training to understand the idiosyncrasies of the dementia patient (7).

A day care program provides three to six hours of structured activities and supervision for the ambulatory Alzheimer's patient and respite for the family and home attendant. Family members report that patients are in a better mood after day care and express their eagerness to return either by saying so or by dressing early. Sometimes with prompting, patients can recall some aspects of the day, thus promoting conversation around a new, positive experience shared by both. This can help revitalize their relationship. Day care also allows family members to observe and model their own efforts at managing the patient after the responses of the staff. Though not living in the same household, a son who was closely involved with his father needed contact with the social worker to help sort out actions he did not understand.

Case History. The son called with a "perplexing and embarrassing question." He routinely took his father to dinner. During the last few times out, his father acted strangely in the restaurant. At times he would order appropriately but did not know what to do when the food arrived. Other times, he would stare at the menu, could not order, but ate when food came to the table.

Distraught and losing patience, the son was invited to observe his father at Day Care. As they toured, the social worker said, "We dance with the participants." To the son's puzzled look, the social worker explained, "Our staff responds to your father by following him, and when he changes steps, so do we."

The son was encouraged to examine realistic expectations for his father's social performance and think about the importance of dinner at a restaurant. Could the demands of an unfamiliar setting make his father more anxious? What other significant social experiences could they share?

The son spent several hours at Day Care, observing his father's mood and behavior changes and the staff's responses. When his father abruptly stood up and walked out of an exercise group, he was quietly called back. Sometimes, the father acknowledged the worker's request and returned in a few minutes to resume the exercises. His refusal to attend a clinic was handled by the nurse moving away and returning in a few minutes with the same request. The day he stared at his lunch the aide responded by placing the utensil in his hand and demonstrating a motion to eat.

Staff members have learned to "follow" the patient and share with each other what is effective. At times, they must begin an interaction by leading or demonstrating the request.

Counseling Family Members. Managing the Alzheimer's patient at home is difficult because of the irrational progression of the disease as well as the quality of the patient's past relationship with his family. The caregiver's own personality, age, health, finances, and environmental realities (family support and community services) also have an impact. In session, many spouses express anger, sadness, and bitterness that this has happened to them. They resent that plans for their last years are being destroyed and worry about expenses and the prospect of a pauperized future. There is annoyance with the perceived indifference of doctors, dissatisfaction with dependence on home attendants, and disappointment with family and friends who seem to be abandoning them as the illness steadily worsens.

For some families, self-help books such as those by Mace and Rabins (8) and Powell and Courtice (8) offer invaluable explanations of the disease, emotional support, and sound practical suggestions for coping with unrelenting needs and, at times, infuriating demands. *The 36-Hour Day* wisely cautions the reader to decrease and simplify those situations which might provoke a "catastrophic reaction" from the patient. These precautions can amount to rearranging one's home—putting up signs, installing gates.

Other caregivers make use of the information intellectually but have great difficulty integrating it emotionally. Conflict within themselves and with many external stresses may strain their capacity to make optimal use of self-help guides. During social work counseling, spouses and children may demonstrate an ability to deal with the patient but fail to protect themselves from their own "catastrophic reactions" to this new role.

If a wife can afford to hire a home attendant for respite, she may find herself sharing her home with two strangers: a husband who no longer recognizes her and an attendant whose housekeeping habits she experiences as intrusions. The underlying distress, expressed as "I'm sick of coming home and turning on the radio and hearing that terrible music or burning my toast because the setting was changed," can escalate to "This will only end when one of us is dead!"

The wish for the patient's early death is often expressed in a desire to trade Alzheimer's disease for "cancer." However, the family members cannot psychologically tolerate these wishes for very long, and considerable guilt develops, leading to greater self-sacrificing behavior (9).

How much family members can tolerate repetitive, incoherent behavior and cognitive degeneration varies considerably. When meaningful verbal communication and even recognizable gestures disappear, caregivers relinquish the customary rewards for helping a sick loved one. Instead, their tireless ministrations are greeted with hostility, suspicion, or indifference. Relatives who do not agree with the decision to keep the patient at home may defensively withdraw recognition and praise: "You wanted to keep her at home. Don't tell us how difficult it is!" Finally, despite all efforts for months and years, the disease progresses, decimating the patient and leaving caregivers feeling ineffectual. This helplessness is often a severe narcissistic injury to their self-esteem, which has already become vulnerable through the normal process of aging.

As the symptoms advance, it becomes impossible to deny the loss of the loved one. Yet the person is not dead. An appropriate mourning process is impeded; thus the spouse or child is deprived of the opportunity of working through the attendant emotions of remorse, ambivalence, and relief and is prevented from cathecting to new objects. A man whose wife had been institutionalized for three years agonized over his close friendship with a widowed neighbor. Another, depressed and withdrawn, mentioned his inability to watch television or to go to a movie in the past two years.

Weekly individual counseling with the social worker addresses these issues and is the most direct intervention in helping caregivers to cope. Since the dementia patient's continued functioning in the community depends on a spouse or child, these sessions help reduce their stress so they can continue to give care (10). The fear that the disease might be hereditary permeates the sessions with children. While a child wonders, "Can it happen to me?" a spouse cries, "Why did this happen to me?"

Case History. A 72-year-old woman has been married for 51 years. Her 80-year-old husband is moderately impaired and attends day care. Their three children advised placing him in a nursing home, a decision she rejected because of financial consequences and emotional conflicts. She has seen the social worker in individual weekly sessions for two and a half years.

Despite informing herself about the disease and occasionally attending support groups, she described herself as immersed in a cycle of impatience, rage, guilt, and recrimination. As a therapeutic alliance developed, she began to move away from recounting the daily trials and tribulations associated with caring for her husband and to reveal her own underlying depression and fears of aging.

After several months, she recognized that her husband's irrational actions and personality characteristics, now so evident, had been developing for years. She began to understand her current reactions as delayed explosions from decades of suppressed resentment at deferring to his self-centeredness. Today, when he feebly asks which tie looks best or becomes anxious about her leaving the house, she feels enraged or compelled to recite her age and refuses to account for her comings and goings.

Through counseling, she now knows she is reacting to her own past grievances more than responding to his current confusion. As his condition deteriorates, knowing the sources of these displaced reactions helps her gain greater self-acceptance and control over her impulses. Although managing his care remains the center of her daily living, it is no longer the total focus of her existence. She can seriously consider institutional placement without the same intense guilt or sense of failure and is able to make appropriate financial arrangements for her future.

Institutions

Applications to the institution may remain in process for one year. Family members caring for Alzheimer's patients find it important to keep in touch with the admissions department social worker, either once a month, every few months, or when a crisis arises. Most often, the family member is seeking some contact and the chance to share frustrations. The social worker can provide the recognition that the caregiver may not be receiving from the patient or other family members. Caregivers also seek advice for entitlements and assistance with interim planning, such as day care, before institutionalization.

The social worker assesses other factors affecting the family's ability to maintain the patient at home. Already feeling unappreciated, the caregiver confronts behavioral stressors, such as the patient's incontinence, violent mood swings, and inappropriate sexual expressions (11). As the patient's demands exceed the family's capacity to cope and as role expectations are further blurred (12), placement becomes a painful but necessary consideration. However, institutionalization can be impeded by a shortage of facilities or by the family's inability to decide.

Case History. An application in process for one year was opened by a woman while her husband was in Day Care. At age 72, he was ambulatory but with severe dementia. His erratic behavior, his total dependence for activities of daily living, and the lack of any gratifying interaction made care unmanageable for the wife. The couple had a son in California who could not accept his father's deterioration and a daughter in Boston who was sympathetic but ambivalent. The wife's weekly sessions with the social worker centered on her conflict about placing him in the nursing home.

She appeared to be coping with caring for her husband by developing cardiac distress requiring periods of hospitalization for up to two weeks. With the wife in the hospital, the social worker increased the husband's day care attendance to five days a week and would arrange for his elderly sister to care for him.

After returning from her third hospitalization in nine months, she arranged for a preadmission physical for her husband. During the exam, she had severe chest pains and was rushed to the hospital, where she remained for three weeks. The Day Care social worker intervened on three levels: (a) enlisted the wife's doctor to help explain the relationship between her cardiac distress and the burdens of caring for her husband; (b) helped the children mobilize themselves to return to New York to be of support to her; (c) counseled the man's sister to tell the wife that she could not be a back-up person during these hospitalizations.

The man entered the institution one month after his wife was discharged from the hospital. She felt some immediate physical and emotional relief but appeared grieved and depressed. Rather than completely relieving the problem, nursing home placement changes the nature of the burden for family members.

During the application process and following admission, the social worker must assess the relationship of the spouse or children to the patient. Latent family problems emerge with institutionalization. When displaced onto the staff of the facility, these unresolved problems interfere with care. If the patient remains agitated under the staff's management, the family is angry at the institution for not making him better. If the institution manages the patient, the family is upset that staff has accomplished what they had failed to do.

Alzheimer's patients coming from their homes demonstrate a range of awareness of the trauma of being separated from familiar faces, voices, and surroundings. Stress, fear, and the absence of environmental cues exacerbate their restlessness and confusion. It is important that the family member who was the primary caregiver be available in the transition period from home to nursing home. Visiting at significant times of the day (clinic appointments, for example) is encouraged. This way, the staff can observe and learn from the interaction between patient and family members. Despite exhaustion, the spouse or child who cared for the patient for many years has developed a litany of responding techniques for the irrational demands and specific needs of the patient. Management in the institution may initially depend on tapping and understanding how the family gave care. The following anecdote illustrates how this information can be combined with professional expertise:

> During an admission interview, the social worker suggested to Mr. S. that he remove his coat. He sat and stared. Mrs. S. repeated the order. No response. Looking directly at her husband, Mrs. S. gently said, "Jack, take off your coat," and demonstrated removing the coat. Mr. S. stood up and took off his coat. Mrs. S. smiled and commented that he was always stubborn. At a follow-up meeting, the floor staff discussed Mrs. S.'s skill in responding to her husband through patience, gentle voice, eye contact, and use of mimicry.

Although concrete tasks are surrendered to the nursing home staff, experience has shown that families need a role within the institution that includes participation in patient care (13). The social worker counsels family members and helps determine how they can effectively continue their caring relationship with the patient. These roles are developed around former relationships and the needs of patients and family members. Children's participation will depend on their closeness and involvement with a parent. A spouse who cared for the patient at home may find it particularly important to feed him and escort him to programs. Those who cannot visit frequently will engage a companion for a few hours a day to provide more personal attention.

"The institution is often blamed by the family for the appearance of affects that have, in reality, long preceded admission" (14). Meetings with family members can promote appropriate interaction with the staff. An interdisciplinary meeting following placement provides a setting for family members to express their concerns and expectations and the staff to discuss the kind of care the institution can provide. Delicately orchestrated by the social worker, this open dialogue allows both groups to listen and set in motion a plan for future communication.

Because Alzheimer's patients are difficult to manage and require a safe area to wander, institutions are reluctant to accept ambulatory patients. Providing the bulk of the daily care, the ancillary staff is confronted by their inability to understand these patients' specific needs. They will then react instead of respond to erratic actions, resulting in a paradigm of frustration, burn-out, and poor care. "Staff training in work with the senile aged must consist in teaching staff how to observe and understand the aged person's action and behavior" (7).

Learning to respond means that the staff must pause and think of another way to answer an inappropriate or repetitive question. They have to take a few seconds and demonstrate what they want the patient to do. For example, if Mr. J. refuses his medication the nurse can encourage him to mimic her gesture of raising a cup to her lips and "telling" him to drink. Cultural cues can be very useful. A recreation worker has successfully assisted a patient to drink his juice by raising a cup and saying "L'chaim [To your health]!"

Helping also includes teaching professional and nonprofessional staff to set short-term goals and have limited expectations for the patient's progress in treatment and recreational activities. The staff should be encouraged to individualize their responses, noting what works and what does not. What may prove effective in providing care and programming one day may not the next. "I know John pretty well," said an orderly to the social worker. "Some days, when I direct him to the dining room and he gets that funny, nervous look, I take him back to his room and bring him his tray. I don't push, then he's okay." How does the orderly know enough about John to make a differential assessment? At a meeting with the social worker and the orderly, John's daughter shared facts about her father's personality and how she cared for him. With this information, the orderly was encouraged to try out different approaches in responding to the patient.

Does It Really Matter If It's Tuesday?

The wisdom needed to steady and support the caregivers must come from their own courage to answer, "No!" to the painful question, "Does it really matter if it's Tuesday?" (15). Answering "no" does not mean giving up on the patient, contributing to his decline, or being neglectful. It is an approach that follows the patient's endogenous rhythm, requiring a patient-centered set of expectations.

Reality orientation and cognitive stimulation are necessary to maintain levels of functioning in early or middle dementia. When the assessment indicates severe cognitive decline or late middle dementia, helping the patient perform necessary routines is more important than explaining time, place, or activity. Eating is a necessary routine; understanding that the meal is breakfast or lunch is not important to the patient. The family and staff who insist that the patient knows which meal he is eating are asking the patient to function in the caregiver's world of reality.

A leader of an Alzheimer group trying to extract the word "Thanksgiving" through the use of reality cues is thwarted when one patient calls out "Christmas," echoed by others. Since they will probably not recall the group's discussion, responding with "Mr. K. is thinking of Christmas; isn't Christmas a cheerful holiday" validates the patient's response. To "correct" his answer may embarrass Mr. K. and be futile for the leader. Even an incoherent mumble can be acknowledged with an interpretation of the patient's feelings, particularly when the psychosocial history is known (16).

Individual contact between parent and child is disturbing when recognition is absent. Momentary recognition, although confused, can be related to an experience associated with pleasure or comfort even when memory is impaired. Appreciating the value of a gesture or word and responding within the context of the patient's reality will lessen the caregiver's anguish. Trying to communicate with her mother, a 60-year-old woman shouted, "I'm your daughter Ellen, not your sister Clara." The social worker turned to the patient and said, "Your daughter loves you," while pointing to the daughter. The patient repeated, "My daughter loves me." Asking Mrs. B. what made her think of Aunt Clara might bring a coherent reply, or just a mumble or a stare. Stressful situations can be reduced if it does not matter who is being acknowledged or that the question went unanswered. It may be more appropriate to respond with, "I love you, mother," plus a demonstrative hug and kiss. The spirit of the interaction has to rest on the notion that it really does not matter if it is Tuesday.

As research progresses, more will be learned about the nature of the disease and specific therapies devised for the patients. Until then, we must learn from Uzzah's fate and direct our efforts and support to the caregivers who need our help.

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Introduction

David B. Sachar, M.D.
Guest Editor

The Future of Gastro-Enterology

This special section is dedicated to the man who founded academic gastroenterology at The Mount Sinai Hospital and who continues to illuminate academic gastroenterology throughout the world—Dr. Henry D. Janowitz. Director of Mount Sinai's Division of Gastroenterology for over 25 years, past president of the American Gastroenterological Association, and recent winner of that association's highest honor, the Julius Friedenwald Medal, marking a lifetime of distinguished service to the profession, Henry Janowitz unburdened himself of his administrative duties as division chief in 1983 and has become more active on all other clinical and scholarly fronts ever since.

On December 18, 1985, The Mount Sinai Medical Center convened a Special Symposium on the Future of Gastroenterology in honor of Henry Janowitz. The symposium was jointly sponsored by the Friends of Digestive Diseases Research at Mount Sinai and by the Burrill B. Crohn Research Foundation, Inc., with the aid of an educational grant from Pharmacia Laboratories. Following introductory remarks by Medical Center President James Glenn and Dean Nathan Kase, who both praised Dr. Janowitz's achievements and his continuing productive career, major addresses were presented by three luminaries of academic gastroenterology.

"The Future of Gastrointestinal Immunology" was discussed by Dr. Warren Strober, chief of the Mucosal Immunity Section, Laboratory of Clinical Investigation, National Institute of Allergy and Infectious Diseases, National Institutes of Health. "The Future of Clinical Gastroenterology" was foretold by Dr. Thomas P. Almy, Professor Emeritus of Medicine and of Community and Family Medicine at Dartmouth Medical School. Finally, "The Future of Molecular Biology in the Gastrointestinal Tract" was considered by Dr. Kurt J. Isselbacher, Mallinckrodt Professor of Medicine at Harvard Medical School and chief of the Gastrointestinal Unit at Massachusetts General Hospital. Two of those three lectures are published in this special section.

The section concludes, appropriately, with a paper by Henry Janowitz himself. He delivered it at the nation's oldest continuing gastroenterological society, the Milwaukee Gastroenterological Association, and also at the Scott and White Medical Center in Temple, Texas, on the occasion of the inauguration of the Nicholas Hightower Chair in Gastroenterology. Dr. Janowitz's commanding position today and his enduring influence on the future give him a sweeping vantage point from which to survey "Gastroenterology in the United States, 1935–1985." He continues to honor all of us with his ongoing work.

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The Future of Clinical Gastroenterology

Thomas P. Almy, M.D.

When Doctor Sachar invited me to join in doing honor to Henry Janowitz, and in celebrating his accomplishments, I hardly let him finish—I joyfully accepted. When he then asked me to forecast the future of clinical gastroenterology I was assailed with doubt that I would do justice to the expansive opportunity he presented. But the anticipated pleasure of this occasion swept me along.

I'm not surprised that this whole program is future-oriented. What could be a more appropriate salute to Dr. Janowitz? This young man has always looked to the future. As president of the American Gastroenterological Association (AGA) he commissioned a thoroughgoing projection of the future of that society by a blue-ribbon committee, as a result of which he brought about changes in its membership which have shaped its subsequent course (1).

What I can offer is a personal view, and I hope for your indulgence as I try to fill in a large canvas with broad strokes of the brush. I ask you to consider the present and future of gastroenterology in terms of the social and economic context of medicine in general. Believing that those who would predict the future must examine the past, I first briefly review the forces that have led us to our present position.

Some Cultural History

Anyone who has studied the monumental work of Paul Starr, *The Social Transformation of American Medicine,* must have been impressed with the great and rapid changes in the social role of the American physician over the last 200 years, and must have reflected on the relatively short period of ascendancy of medicine as a "sovereign profession" (2). The early years of this century were marked by rapid advances in the control of infectious diseases, and residual fear of their menace; by high expectations of science and education, and a belief in the perfectibility of humankind.

The belief in the assumption of human progress survived ten years of global depression and six years of the most horrible and destructive war in history. The society that had spawned the League of Nations stood upon its ashes in 1945 and forged the charter of the United Nations. In the same year it unleashed an enormous burst of pent-up economic and technological energy aimed at long-range human betterment. Economists have described what followed as a "long wave" of global development, a sustained tidal wave spreading outward from seismic forces whose epicenter was in the United States. The lessons, the discipline, the technology of World War II would now be put to constructive use. Swords were turned into plowshares, Flying Fortresses into DC-4's and DC-7's; and the search for chemical warfare agents led to cancer chemotherapy. The explosion of biomedical knowledge was reflected in new red-brick buildings in Bethesda; for their purposes Congress year after year appropriated more research funds than had been requested. When the burgeoning research effort led to the virtual eradication of polio, expectations for disease control ran higher than ever before.

Gastroenterology entered this postwar picture relatively late. Dwight Wilbur, in 1955, was the first president of the AGA to devote his entire address to the state of research in our field, and to establish a standing committee on research (3). About then, when Dwight Eisenhower was be-

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lieved to have Crohn's disease, the NIH discovered the digestive tract and began to support graduate training programs in our field, and the pace of gastrointestinal research began to quicken.

But the public's expectations grew ever more rapidly. In the 1960s, the Great Society sought to provide equal access to the benefits of scientific medicine for all citizens, whatever their ability to pay. Our profession was to be relieved of its ancient self-imposed obligation to care for the poor without fee, and tax money would be used to pay us and our hospitals at rates we regarded as customary and reasonable. This blank check, at a time of inflation, burgeoning technology, and popular demand, was to prove a historic miscalculation for all concerned. This and other national programs were launched when the position of the United States in the world economy was already declining. After 1971, the U.S. became more of an importer than an exporter, especially of oil; and soon thereafter, more of a debtor than a creditor in world markets. Suddenly it became customary to count the costs of things. For the first time we began to hear, in discussions of medical care, that resources are finite. The tidal wave of support for scientific medicine began to weaken, and countercurrents developed.

Repeatedly from 1967 onward we in gastroenterology assessed and then publicly declared the high social and economic impact of digestive diseases in the United States, seeking to secure for our field its reasonable share of public recognition and support. We found that, among various categories of illness, the most common reasons for being treated in a hospital are related to digestive disease; we noted that because of the disability produced by these diseases and their high costs, in the total economic burden of illness they rank just after heart disease and trauma. Early on we described a shortage of manpower—a condition that was soon corrected as training programs proliferated and sales of endoscopes rose in logarithmic fashion. Although increases in manpower and available technology offered better care for our patients than ever before, and through the efforts of a few devoted allies public awareness of digestive disease has increased, public support has come slowly because the tide is running against us.

The Current Climate for Medical Specialists

In the present climate, we are particularly vulnerable because our costs are high and our manpower has increased so dramatically. Both the lay public and the Congress are troubled by what they perceive as an oversupply of medical subspecialists, providing expensive services unevenly because they are unequally distributed in relation to population. Congress, aware that 70% of the cost of health care is expended on our orders, sees costs as directly related to our numbers. They favor restrictions on training both at the undergraduate and graduate level. So when those many colleagues of ours have climbed Capitol Hill to speak of our efforts to control digestive disease, they have often met the overall objection that health care costs must be reduced to make way for other human needs—education, welfare, public safety, and national defense—in a massive zero-sum game.

So we find ourselves, the adherents of perhaps the oldest organized medical subspecialty, perceived as human resources in a vast, governmentally regulated service industry.

Our Job Descriptions and Social Role. At times, the control of our future seems to be slipping from our hands. If we would prevent this from happening, would we not do well to reexamine our job descriptions and reassert our own convictions of our role in society, taking into account all our qualifications and the needs and expectations of the public? Historically, we as well as other medical subspecialists have served both as expert consultants and as direct providers of continuing care for chronic illness. How will we choose to combine these roles, and in what proportion?

There are strong indications, from the manner of administration of DRG's and the growing influence of HMO's and other capitation schemes, that both the price and the frequency of utilization of consultants' services and salient, easily identifiable technical procedures will be increasingly controlled. The decision to utilize such services is more and more assigned to the generalist, the "gatekeeper." Gatekeepers, obeying the rational principles of economics, will probably increase their market share by reducing access to specialist services and—when such services are needed—by shopping for discounts in the buyer's market which would result. By the same process, HMO's have reduced hospital admissions of their patients by 30% or more, and many hospitals are looking at empty beds. The prospect of similar inroads on the utilization of consulting specialists should suggest that we tone down this part of our job description.

Specialists and the Uses of Innovations. Mind you, I have not the slightest doubt that our established role in the translation into better medical care of the unfolding scientific advances in gastroenterology will remain important as a service to the public and a source of satisfaction to ourselves. The momentum of research in digestive disease is still strong after over a decade of fighting the ebb tide of federal support. Serendipitous outcomes of basic investigation, like those that gave us the Australia antigen and oral rehydration therapy for diarrhea, will continue to give rise to new clinical strategies. New clinical observations, like that which gave us the gluten-free diet, will soon render obsolete the older theories in our textbooks. While many of the future innovations, like those of the past, will be applicable by nonspecialists, our expertise will be needed to assure that innovations will be used well. If you doubt this, I need only mention the current misuse of cimetidine by the medical profession. How could this product have become the world's no. 1 prescription drug, if the valid indications for its use had been responsibly observed?

Expanding Our Repertoire in Primary Care. Clearly, we have an incompletely fulfilled opportunity, and indeed an obligation, to apply our knowledge and skills in the long-term management of common, chronic digestive disease, even if it involves our assuming the role of personal physician in primary care. Our formal qualifications for this role are incontestable—most of us are certified by the American Board of Internal Medicine. But if we, as well as other specialized internists, are to be credible and effective in this role, I doubt that we are now optimally prepared. Let us listen to comments often made by patients (though usually, of course, about *other* physicians) and ponder what they're telling us.

"My doctor says my condition is very common . . . doesn't sound very interested.": OK, the doctor was tired; that day he had already seen five other patients with nonulcer dyspepsia or habitual constipation, or whatever she had. But our residents and trainees have often got the idea from us that as highly trained specialists we are here to handle the esoterica, the fascinomas, the "interesting cases." Can we afford not to be interested in the common ones?

"My doctor doesn't seem to listen to me, and doesn't explain enough.": Amid the time pressures of busy practices and training programs, skills in communicating with patients are often underdeveloped. Yet nearly all our primary clues come from the history, on the basis of which we proceed, with what patients may regard as unseemly haste, to perforate them with needles, thrust tubes down their throats, or expose them to ionizing radiation. When with apparent satisfaction we announce that the results of all these expensive procedures are negative, how often does the patient gain, not reassurance, but bewilderment?

"My doctor says there's really nothing wrong with me, but to come back in two months.": *Of course,* the doctor didn't say that—but because no understandable explanation of the illness was advanced, and no inquiry made into the anxiety-ridden domestic conflict which was the real reason for his visit, the patient next consulted a chiropractor. We recognize that psychosocial factors play a large role in at least half of our patients' illnesses—are we as well prepared to deal with them as with so-called organic disease? Even Rudolf Virchow and Abraham Flexner referred to medicine as a social science, yet one rarely finds, among the hundreds of abstracts submitted to our national meetings, a paper solidly based on behavioral or social research. Our familiarity with developments in this field is not so good. Now our knowledge of the neurobiology of the gut is growing rapidly. Can we correlate it with human behavior, and find a deeper understanding of functional disorders? Can we learn to apply behavioral methods to the relief of substance abuse, which so often confronts us in the guise of cirrhosis or esophagitis or hepatitis or AIDS?

"My doctor says all the tests are negative, and she wants me to try a new drug. But I heard about the drug on the tube and they called it 'controversial.' ": The public is more than slightly aware of the often uncertain basis of our judgment. They read Ralph Nader, they read package inserts, and they ask for second opinions. Yet we are not involved as often as are our British counterparts in clinical epidemiology and randomized trials. We have not been as active as some other specialty groups in achieving and announcing consensus on diagnostic standards and effective treatment. To do more of this is one of the unfulfilled recommendations of Dr. Janowitz's 1974 Committee on the Future of the AGA. Now legislators, insurance executives, and business leaders have examined John Wennberg's data on "small-area variations" in rates of hospitalization, surgery, and endoscopy for stated conditions (4). They are impressed that, because of unresolved uncertainty of medical decisions, there are wide variations in the utilization of some of our common procedures not accounted for by measurable differences in prevalence or outcomes of disease in various communities. There is danger that, despite Wennberg's insistence to the contrary, third-party payers will decide that the lowest levels of utilization of these services are the *right* ones. Is it not urgent that we follow the lead of several medical associations, now including the AMA, in reviewing our own performance in these terms?

These are some clearly audible concerns of the public about their health care which result, I believe, from the present conditions of medical practice and the climate of our education and professional training. I wonder what would happen if these concerns were adopted as an agenda by clinical gastroenterologists, and pursued in continuing education programs, in new forms of research, and in the apportionment of professional time and effort. I believe it would profoundly affect the future of our field.

A Retrospective Review for Subspecialists In the Year 2000

Here are some possible outcomes as they might be reviewed retrospectively in a presidential address before one of our societies in the year 2000.

House Calls and Home Care. It was about 1985, you will recall, when almost all medical subspecialists, gastroenterologists among them, acknowledged that their numbers had generally outstripped the real needs of the population for technical procedures and expert consultation in their fields, and that they were already spending as much as half their time in the role of primary care physician. They applied themselves to learning from the disciplines of general internal medicine and of family medicine, which with the labels removed proved to be amazingly hard to distinguish from each other.

Like these other generalists, we in gastroenterology have learned to make house calls, especially on our elderly patients. But we have learned to delegate a lot of these calls to the nurse practitioners we have taken on as office partners—just one example of our increasingly respectful cooperation with independent practitioners in other professions. This became essential when, with improving techniques for conducting treatment regimens in the home and still further escalation of hospital charges, the hospital technology of the 1970s and 1980s became the home care of the 1990s.

We have found in the course of this period a large measure of satisfaction in the management of common disorders of still uncertain origin, in which the striking progress of the last 15 years in fundamental biology has not yet greatly altered the daily tasks of diagnosis and treatment. Our satisfaction increased at first because, for a while, we had fewer patients and more time to talk with them. We learned to use the details of the history quantitatively, aided by desktop computers, to estimate the prior probability of getting decisive information from invasive diagnostic procedures. The work of deDombal (5), Wasson (6), and others on clinical decision rules was widely replicated, and as a result an average of about 30% of the overall costs of ambulatory care has been saved by limiting endoscopic and imaging procedures to patients with medium-to-high risks of having treatable organic disease. At the same time, the satisfaction derived from doing these procedures, now more often fruitful than they once were, has vastly increased.

Communicating with Patients. As we begin this new millenium, the youngest of our colleagues in the practice of gastroenterology have emerged from their medical school and residency years much better prepared for this pattern of practice. In the wake of the report on Global Professional Education of the Physician in the early 1980s, curriculum changes in most schools afforded students much better coaching in communicating with patients (7). They were routinely monitored by videotape. They know more than we did, as residents, about the principles of the behavioral and social sciences which determine clinical effectiveness. We, their elders, learned much from them on rounds, and sharpened our skills further in hospital staff conferences and continuing education courses. Perhaps, from our earlier experience, we can appreciate even better than the residents the value of this training. Our histories are better. We have fewer problems with patient compliance (and we more surely know when there *is* a problem!). We are more effective in dealing with harmful habits and needed changes in lifestyle; to this end, we spend more time with members of our patients' families, who give valuable help in their care. We now work closely with patients' mutual support groups, and with psychologists in programs of behavioral modification.

Clinical Records. Our clinical records have changed in important ways. We now use automatically coded and recorded history questionnaires and psychological rating scales, and voice-activated remote word-processing of consultation notes. Our coded diagnoses include both etiologic and morphologic categories and routine, abbreviated assessments of functional status. These assessments, which may include activities of daily living, mental status, economic status, and social supports, are of course often required of us as a measure of outcome, and serve to expedite needed social services. Much more often than they were two decades ago, our records are used in randomized trials, in surveillance of persons at risk for certain diseases or complications, and for ongoing calculations of benefit/cost margins.

Health Care Research. Though we still have a pluralistic system of health care, the increasing number of physicians who work in incorporated groups, for patients enrolled in prospective payment plans, have become in effect corporate planners, working partners of our lay administrators in one of the most complicated tests of operating efficiency that industry has ever seen. The quality of our records and the continuing research based on them, in which so many of us are involved, have been key factors in this efficiency. We keep track of variations in the rates of hospitalization and the utilization of major procedures by community and by hospital or service plan, as Wennberg (8) began to do in the early 1970s, to detect and deal with areas of uncertainty in medical decision making.

Successful Screening for Colon Cancer. Although this effort in health care research was motivated originally by the desire to pinpoint areas of waste and to control costs, it has had other and very different consequences. For example, we at last were convinced, by the final reports of the New York (9) and the Minneapolis (10) studies of population screening for colon cancer, that colonoscopy on positive Hemoccult reactors, with polypectomy when indicated, drastically reduced the incidence of colon cancer. We at first doubted we could apply such screening uniformly to consenting adults over the age of 45, because it would require almost a million colonoscopies, by over 2,000 endoscopists, at a cost of nearly half a billion dollars each year. But when it was realized that this sum approximated the cost of care for all the clinically recognized colon cancers that would otherwise have developed, the policy received a green light from even the most tight-fisted HMO's. I'm sure you would agree this is a major factor (along with the new method of recognizing tumor DNA in stools, that we call in the vernacular "Hemoccult V") in the rapidly approaching disappearance of this devastating disease. On the other hand, we have had to respect the cold hard results of other cost-benefit studies, and have sharply narrowed the indications for some of our procedures and consigned others to the scrapheap.

Effects of Fiscal Constraints on Health Care. Let us confess how vigorously we at first fought these fiscal constraints. We resented these intrusions on our professional judgment, and we disliked being forced to deny anything to our patients. But we remained their firm advocates even while we were forced to bow to the public demand that health care be less expensive so that taxes remain low even while the national debt was being reduced. We knew, when the Gramm-Rudman Act to eliminate the federal deficit was passed back in 1985, that much of the cutting of expenditures would come out of Health and Human Services. When we were told that for health care to consume over 10% of the GNP was intolerable, it did no good to respond that our lavish transportation system was even more expensive, costing 50% more for private automobiles alone than did all of health care.

Boom and Bust in For-Profit Medicine. Worse than this, the regulation of expenditures for health placed few restraints on free-market competition, and the for-profit sector became fat and either forced out or bought out nonprofit hospitals and service units in thousands of communities. The great chains, in consideration of their stockholders' interests, found various devices for reducing services to the indigent; but soon there were in many cities no other facilities to which the poor could be transferred, and the for-profit hospitals in those cities were closed because they were not profitable. The reaction to this, you will recall, began in Indiana in 1991. The state withdrew the authority of these chains to operate hospitals, and that reaction spread like wildfire to other states.

The details of the crisis when the bubble burst on for-profit hospitals and the corporations went belly-up are too numerous, too recent, too painful, and too familiar to recite here. But let us not forget the key importance of physicians' practice groups, of county societies, of the medical boards of erstwhile not-for-profit hospitals, which cooperated with present and former hospital trustees to reconstitute a workable medical service system in record time. I hold that the exercise in accountability and group process to which we were forced earlier in the budget crunch enabled us to respond effectively and to earn the high esteem in which we are now regarded by the public.

Fees for Cognitive Services. Let me close this account by reminding you of one other most significant change in the climate of clinical gastroenterology and other fields of medical practice. So many of us are now paid by salary or by shares in our groups' earnings that we are less conscious of individual fees-for-service than we used to be.

But the economic incentives generated by fee schedules, by relative value scales, have always influenced our patterns of practice, either by our direct perceptions or by the pressures of our health plan administrators. The old fee schedules prevalent in the 1980s rewarded specialists in our field much more highly for doing procedures than for so-called cognitive services; we were constantly under pressure to limit our time in talking with patients in order to make ends meet for ourselves or our groups. And it bothered us, because in that talking were the elements of good diagnosis, of patient education, of compliance. Then in 1985 HCFA awarded a contract to a team at Harvard to develop a new relative value scale based upon the resource costs—the time, the complexity of services, the investment in education and training, and the office overhead—of the physician.

So now we are rewarded as much and as well for our judgment and analytical skills as for most procedures. I wonder if anything has ever done more to help us enjoy patient care. Even the crocks seem interesting. We spend more time explaining things. The patients, proud of knowing us better, speak more positively about us to their friends. Would you not agree this was one of the principal factors in easing the malpractice crisis, and in bringing to an end the pressure for defensive medicine? Just about that time the media began to carry story after story about the excessive fees, the oversupply, and the maldistribution of lawyers in the United States.

Summary

I have tried to view the future of clinical gastroenterology, like its recent past, as profoundly influenced by the forces which shape the nation's purposes and by the tides of public opinion. If we are to prosper as much while part of a major industry as we did when we were a "sovereign profession," we will have to adopt the strategy of "marketing," which I understand to mean anticipating the needs and wants of the public. I submit that the greatest current need of the public we can satisfy is the need for wise and responsible long-term care of their chronic digestive diseases.

As so often in the past, after formulating these thoughts I found that they had been expressed earlier and more succinctly by Henry Janowitz. A few years ago he wrote:

"A gastroenterologist is a physician who knows how to *think about* and *manage* the gastrointestinal problems of his patients. It has taken too long, and too much effort for us to allow this concept to disappear, and return to the idea that we are technical experts, now armed with supertechniques" (11).

By reasserting this emphasis, I hope I have persuaded you that the future of clinical gastroenterology can be one of no little excitement, and a large measure of satisfaction, for its practitioners.

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The Future of Gastrointestinal Immunology

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If we gastroenterologists have a future as illustrious as the past Henry Janowitz has created, our future will be very bright indeed. One of the things he has taught us is to look at inflammatory bowel disease in all its clinical and therapeutic complexity; that lesson should be extended to the task of trying to understand its cause. Perhaps one of the blocks to understanding the disease is that we tend to simplify an entity that in fact has a number of different causes or possibilities as idiopathologic events.

I want to dwell on gastrointestinal immunology in general and to convey some of the excitement, some of the new things, some of the trends in the field, and finally, to relate this field to the understanding of inflammatory bowel disease or Crohn's disease in particular. We have a rather large task: to talk about cells, how they interact in the gastrointestinal tract and in the immune system in general, and how they may interact with each other on the molecular level. These are the two themes to center on in exploring the forward motion of the immunology of the gastrointestinal tract—the better understanding first of cellular interactions, and second of the signals that pass between cells and how they affect cellular function on the molecular level. I try here to offer some notion of where we are going in that direction.

Cellular Interaction and Function

The very rich lymphoid tissues in the rabbit appendiceal area are similar to tissue in Peyer's patches and not very dissimilar from lymphoid tissues in the human and the mouse gastrointestinal tract. In fact, in the immune system, the lymphoid tissues in the gastrointestinal tract are at least equal in size to the tissue present elsewhere in the body. Not only is this a very large area of lymphoid tissue, it is in fact perhaps the most important area, because it is the area most in contact with the external environment. Overlying these organized lymphoid tissues are M cells, which have been nicely studied by Dr. Owen in San Francisco, and others. These are specialized epithelial cells through which macromolecules pass and enter into Peyer's patches, stimulating cells there. An M cell appears on the surface as a depression in the surrounding columnar epithelial cells; antigenic materials can fall into this pit, then be taken by the M cell and presented to the lymphoid cells within the lymphoid tissue itself. The germinal centers in Peyer's patch, as in the lymphoid tissue, is full of IgA cells—lymphoid tissue specialized to produce IgA. An issue we need to confront is why this immunoglobulin and not others is made in this location.

Although one can think of this organized lymphoid tissue as generative organs, that is, where cells are born, the cells don't stay there very long. In fact, cells that reach a certain level of development very quickly travel from the organized lymphoid tissue to the mesenteric lymph node, and thence to other mucosal areas; this gives the system a name, the mucosal immune system, because it not only involves these generative areas, but it also involves the various receiving areas, the areas that are in fact confronting the external environment.

Looking at villi in the duodenum, we see cells that have reached their final destination from the Peyer's patches in the lymphoid tissue,

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after traveling through the mesenteric node and the thoracic duct. This group of cells differs greatly from the group in Peyer's patches. How do those differences occur?

Some years ago, we at my laboratory took macrophages from Peyer's patches and loaded them up with antigen ordinarily found in the gastrointestinal tract, ovalbumin, then presented these macrophages to prime lymphoid cells and measured the capacity of these cells to proliferate. Spleen macrophages induced proliferation in the lymphoid cells, but so did Peyer's patch macrophages. Interestingly, one can feed an animal ovalbumin on one night, and the next morning harvest the macrophages from Peyer's patches, and then, without adding any additional antigen, put those macrophages in with the primed cells and get this same proliferative response. What does that tell us? That every time we eat, we in fact get antigens in the macrophages of our Peyer's patches, and these macrophages then present antigens to lymphoid cells and stimulate the lymphoid cells.

That easy accessibility of the mucosal lymphoid system creates a dilemma: how does the mucosal lymphoid system maintain its capability of responding to pathogens or other materials that are potentially dangerous to the organism, and at the same time not respond to ubiquitous materials?

Ovalbumin is a ubiquitous material, and by eating it, we are pulsing our macrophages in our Peyer's patches. There must be some mechanism for preventing the system from going any further. Otherwise, the lymphoid system in the gastrointestinal tract would be coopted by rather trivial responses. Thus we have three questions we would like to answer. How does the mucosal immune system regulate itself—how does it solve this dilemma? What is the relation of mucosal immunity to autoimmunity, not only in the gastrointestinal tract, but throughout the organism? And does a disorder of the mucosal immune regulation explain inflammatory bowel disease?

Regulation of Mucosal Immune System. The mucosal immune system regulates itself not by a single mechanism, but by three different mechanisms: direct cell inactivation, suppressor cell elaboration, and induction of antigen-nonspecific suppressor cells. Through this variety of mechanisms, the system in fact is very capable of differentiating friend from foe.

Direct Activation. As for direct inactivation, the gastrointestinal tract is under massive antigenic exposure, and these antigens—they can be food materials, dietary materials of all kinds, bacterial—flood into the system and are also pulsing the macrophages, just as the ovalbumin given to the mice in the experiment. Reynolds and his co-workers have recently shown that the Peyer's patches are much more of a generative organ than we thought. By counting the number of mitoses in this area, he showed that the number of cells developing in the Peyer's patches is much greater than the number of cells coming out through the lymphatics—perhaps nine or ten times greater. This is the exact situation that one finds in the thymus, that is, a tremendous amount of cell generation but really very few cells leaving the area. Thus the Peyer's patches qualify as a central lymphoid organ.

Looking at the same process on the cellular level, we find that for instance, B cells go through a variety of maturational steps: pre-B cell, so-called immature B cell, mature B cell, plasma cells. If antigen contacts the cell in the immature B cell stage, it inactivates or kills the cell, in a process of tolerization. But if antigen contacts the cell in a later stage, the result is cell proliferation and activation. So what one can suppose is going on in the Peyer's patches in this mucosal lymphoid organ is that much of the antigen is contacting immature cells, and the cells are being inactivated. Perhaps nine-tenths of the cells are actually being born in the Peyer's patch and are being inactivated; only a small number are actually proliferating.

This kind of selective pressure by antigens also shapes the repertoire of these cells in the Peyer's patches, because it means that ubiquitous antigens have the opportunity to inactivate cells. Only those cells that have mutated a little bit during the process of somatic mutation, that do not recognize ubiquitous antigens, that do not recognize self antigens, get through, then presumably contact their appropriate antigen a little later on in their developmental cycle, and then become the cells that are disseminated to the rest of the body.

The picture that emerges is that tremendous antigenic pressure is actually selecting cells in the Peyer's patches, only a small number of cells are getting through, and this in part accounts for the phenomenon that you don't respond to everything in your environment.

Suppressor T Cells. In respect to suppressor T-cells as a mechanism of regulation, I draw your attention to an experiment that I think I can call classical, since an experiment becomes "classical" after it is repeated about five times—an experiment first performed by Chase; he fed an antigen to one mouse, and showed that that mouse was responsive to the antigen, a contactant, something testable on the skin. Later experimenters transferred cells from this fed animal to a second animal and showed that the transferred cells rendered the second animal unresponsive. In essence, this experiment showed that the feeding of an antigen induces a suppressor cell in mouse A which can be transferred to mouse B, which will be unresponsive.

Through a great deal of research over the last ten to fifteen years by investigators in various parts of the world, including Benacerraf, Germain, and Dorf, the suppressor cells have been shown to develop not only in the Peyer's patches but elsewhere in the spleen, and are the product of a cellular network. There is a first suppressor cell, TS_1. This creates a product, the humoral factor, which interacts with TS_2, the second suppressor cell; there is the TS_2 factor; there is a TS_3 factor; and so on. This complexity probably relates to the way the system is regulating itself. In 1985 Batisto and his co-workers examined Peyer's patches for this cascade and found two cells present in it, TS3 cells and T acceptor cells. These link the suppressor cell development occurring in the much simpler system with the complex suppressor cell cascade. The suppressor cells developing in Peyer's patches are no different from those developing elsewhere and are part of the sophisticated, complex cellular cascade.

One of the consequences of having not just a suppressor cell, but a suppressor cell cascade, is that eating an antigen, or orally immunizing someone, will produce not only one suppressor cell, but an antigen-specific suppressor cell, an idiotypic suppressor cell, and various related factors, all parts of the complex cascade, because some of these cells recognize not the antigen but the antigen receptor (the so-called idiotype specific suppressor cell). Various investigators have found that after eating, various products are found, all explained by augmentation not simply of one suppressor cell but of a whole cascade. My NIH colleague Steve James has used a fluorescent activated cell sorter, which employs two different fluorochromes, to identify specific subpopulations of cells by the two kinds of specificities on their surfaces. James's study shows that the suppressor inducer cell which is part of the suppressor cell cascade is not in fact present in the lamina propria. So the suppressor cells that develop in, and then leave, the lamina propria are really related to the internal immune system, not to the lamina propria.

Antigen-Nonspecific Suppressor Mechanism. The C3H HEJ mouse strain has the particular property of not reacting to lipopolysaccharide (LPS), a very common material in the environment, material that is part of the bacterial cell wall. These mice do not proliferate in response to lipopolysaccharide. A group of investigators in Alabama headed by Dr. McGee found that these animals had heightened responses to oral antigens, and that their tolerance could not be easily induced by oral antigens using the experimental technique of feeding one animal and passing cells from that animal to another animal. These animals do not develop the inactivation characteristic of other animals. The C3H HEJ animal, which does not react to LPS, has been shown to have a fairly large response to the antigen trinitrophenol, whereas a strain similar to the C3H HEJ in every respect except that it does respond to lipopolysaccharide has a much lower response to trinitrophenol by a factor of 5. So somehow the capacity to respond to this lipopolysaccharide is important in determining the extent of magnitude of an oral response. How can that be?

Dr. McGee has his ideas about how that could be, and I have my own ideas, and I'd like to give you my ideas. What I think happens is that LPS is a very potent stimulus for B cells. LPS stimulates B cells and converts the B cells into B cell blasts. The B cell blasts have on their surface particular activation antigens, one of them being histocompatibility antigens. So this B cell blast has the histocompatibility antigens in greater amount than resting B cell before the LPS stimulation. There is an important class of cells which can recognize its own histocompatibility antigens when those antigens are present in a certain concentration on the cell surface. A subfraction of these autoreactive cells, so called because they are responding to self histocompatibility antigen, can in fact act as suppressor cells and cause feedback inhibition. So the reason why animals that do not respond to LPS give higher responses in the gastrointestinal tract may relate to the fact that these animals do not form blasts in the gastrointestinal tract, therefore do not develop suppressors, and therefore give a higher response.

Note that not only LPS may do this; it is a more general phenomenon, and antigens also activate B cells. I think we will find that this antigen-nonspecific mechanism—antigen-nonspecific because it is set into motion by either antigens or mitogens, yet the cells that result have histocompatibility antigen but cause inhibition through an antigen-nonspecific mechanism—may play a role in inflammatory bowel disease (see below).

Unanswered Questions. These mechanisms—cell inactivation or tolerization, suppressor-cell development, and antigen-nonspecific autoreactive T cells—combine to regulate the mucosal immune system. But a number of unanswered questions remain. First, we still do not know what rules govern a positive or a negative (that is, suppressor cell) response to any particular antigen. Second, are there pharmacologic effects on immunoregulation? This is an extremely important question because we are constantly thinking how the mind, the nervous system, can affect immunologic processes, and recently it has become apparent that certain vasoactive peptides, at least in the gastrointestinal tract, can affect this regulatory phenomenon. Thus we have now for the first time the beginnings of an explanation of how the mental state of a person may affect the immune system and, therefore, an immunologic disease. And finally, the basic question: can a defective mucosal immunoregulation explain inflammatory bowel disease?

IgA Response. Lee Richman in my laboratory replicated the classical experiment first performed by Chase, but looked also at IgA responses, the most important responses in the mucosal immune system. Richman found the same thing others had, and that he had found in previous experiments: a decreased response, a suppressor phenomenon, in IgG in the animal recipient of cells transferred from the antigen-fed animal, as compared to the animal recipient of cells transferred from the saline-fed animal. But this decreased IgG response was accompanied by an increased IgA response.

This result led to the idea that IgA responses are separately controlled, that even in the gastrointestinal system, where the bias is toward development of suppressor cells and to negative responses, positive responses may occur in certain immunoglobulins.

In the regulation of IgA responses, mature B cells differentiate into cells that produce the various immunoglobulin isotypes, in the process of isotype differentiation. These cells then become plasma cells of the particular category. This cellular system has its correlate in the molecular events occurring within the nucleus of the B cell, and in particular, there is an area of the gene which contains the immunoglobulin genes, arranged just as pearls are on a string. During the process of differentiation, when one cell becomes another cell, these genes on a string undergo various kinds of rearrangements to get the final cell. In particular, the various genes that code for immunoglobulins—mu, delta, gamma, epsilon—occur on the string before the alpha. Basically, differentiating a cell to an IgG cell involves getting rid of these genes bringing the alpha gene into juxtaposition with the genes that encode for the part of the molecule that recognizes the antibody, the variable region genes, the VDJ genes. So there is quite a bit of rearrangement and loss of genetic material; the question is, how do T cells affect this process?

Some years ago, we introduced the concept of the switch T cell, a T cell that would be present in the Peyer's patches and cause IgM cells to become IgA cells. Part of this concept was that the switch T cell affected the differentiation of the cell at the molecular level; it was causing a particular kind of arrangement to result in an IgA cell. What we did to try to prove that point is to create clones of cells and mix the clone cells with B cells. We found that clone cells from Peyer's patches mixed with B cells plus LPS as a stimulant produced a lot of IgA cells, whereas clone cells from the spleen did not produce a lot of IgA B cells. This allowed us to say that there was a switch T cell, a cell that caused B cells to differentiate in a certain way. Dr. Mayer at Mount Sinai in New York has furnished additional evidence that such switched T cells do exist and may play a role in both IgG and IgA differentiation.

We have taken this work further by working with both cloned T and cloned B cells, working with a B cell called 7OZ, a lymphoma-derived B cell. If you stimulate it with LPS, more IgM is produced on its surface. Adding a clone T cell doesn't do anything to the IgM. However, mixing this same B cell, 7OZ, with a particular T cell that we derived, the hybridoma T cell called Haj 3, lo and behold, the B cell begins to have IgG on its surface. In other words, the T cell has induced the B cell to produce a new immunoglobulin on its surface, IgG immunoglobulin. We've been able to do a variety of molecular biologic studies and have been able to show that what the T cell seems to be doing is activating the downstream gene: the T cell seems to reach into the nucleus of the B cell and send a signal in to activate a downstream gene, and then the cell becomes an IgA cell.

The interactions occurring between cells are fundamental. They go very deep into the biology of the cell and they direct the kind of DNA rearrangements that are occurring, the genomic configurations and the gene activation steps. T cells also affect IgA cells, perhaps somewhat more superficially. Once the cell has differentiated into IgA-bearing cells, it can produce other factors which expand those IgA cells. The current feeling is that these factors are related to the Fc receptors and the T cell releases class-specific Fc receptors, which then contact the appropriate immunoglobulin on the surface of the cell and expand the cells. So the overall picture that emerges is that, first, there is a switch T cell which causes an IgM cell to undergo certain genetic rearrangements, gene activations, to become an IgA cell, and second, in another cellular step this cell is expanded through factors perhaps related to the Fc receptor, causing terminal differentiation of the IgA cell. Some thing that has always intrigued me is why is there, biologically speaking, an immunoglobulin called IgA? What is the role of IgA? Many people, perhaps 1 in 600 to 1 in 1000, have either very little or no IgA, and these people are for the most part normal people. The other immunoglobulins can in fact perform much the same functions as IgA. I think the role of IgA is twofold. I put forward the idea that the internal immune system has to be protected from external antigens. It doesn't want to see everything on the outside and it does that in two ways; first of all, IgA acts as scavenger to cleanse and filter the system; second, IgA regulation allows elaboration of mucosal suppressor cells which are related to these external antigens and which regulate responses in the internal system if antigen does get in.

In respect to the scavenger function of IgA, we know that IgA can bind to epithelial cells in the liver, and therefore, when IgA forms complexes with antigens that have entered the system, it can escort the antigens directly out through the liver, so the liver acts as an IgA pump. This is a way of reducing the amount of external antigen that gets into the system.

In respect to the second function of IgA, what is the relation of mucosal immunity to autoimmunity? Special strains of mice have been useful in exploring this question. For instance, the NZB mouse develops spontaneous autoimmunity, has many autoantibodies, including anti-DNA, has renal disease and vasculitis, has lymphoid hyperplasia—in short, these animals have much the same clinical characteristics as patients with lupus erythematosus. Interestingly, these animals have a decreased capacity to develop oral tolerance.

The CBA/N mouse has a most useful defect, the XID gene, which affects the immune response. These animals' spleens lack mature B cell populations, which are responsible for responding to polysaccharide antigens, antigens with repeating molecular units. If the genes of the CBA/N animal, particularly the XID gene, is bred into an NZB animal, autoimmunity in the NZB animal is extinguished. This remarkable finding, made by Fred Steinberg at NIH, has important implications for our understanding of autoimmunity. What it probably means is that the cell necessary for autoimmunity is a mature B cell that tends to respond to polysaccharide antigens.

The mucosal immune system of the CBA/N animal, interestingly, lacks mature B cells in the spleen, but has these B cells in Peyer's patches. Furthermore, Peyer's patch T cells allow normal antipolysaccharide responses even in the presence of B cells from CBA/N animals. So the CBA/N animal defect is only a partial defect; given the T cell influence present in Peyer's patches, the CBA/N defect is overcome.

A quite speculative but interesting suggestion is that the Peyer's patch T cell ordinarily produces factors of unknown nature, factors necessary for the final development of the T cells which will respond to polysaccharide antigens, and which will also produce the autoimmune antibodies. One can also suppose, by analogy, that there are also regulatory cells in Peyer's patches, some that induce the maturation of T cells and also some that keep T cells under control and suppress them. So I think what is emerging is that the mucosal immune system has an important role in the development of autoimmunity, not only in the gastrointestinal tract but systemically, because it is in the mucosal immune system that these cells develop and are in fact regulated.

Mucosal Immune Regulation and IBD

Does a disorder of mucosal immune regulation spring from inflammatory bowel disease? I can't answer that question, but I think that what I've said so far allows us to put the matter into perspective. I have talked about the complexity of inflammatory bowel disease, in which the system can go wrong in a number of different ways that lead to abnormal responses and thus to disease: inadequate generation of suppressor cells; more than one cell involved in the cascade of suppressor substances; failure to focus suppressor elements (they can be produced but perhaps can't get to the right place); failure of the nonspecific suppressor mechanism; failure of class-specific regulation (IgA responses being under separate regulation); and improper control of autoimmune clones. Any one of these abnormalities, or a combination, can lead to inflammatory bowel disease.

Some years ago, we at my laboratory showed that taking peripheral cells from patients and normals, and stimulating them with mitogen, produces an interesting phenomenon that constitutes one of the few definite immunologic abnormalities present in Crohn's disease: patients with the disease, especially with early or mild disease, very frequently did not respond to the mitogen in vitro. Normals did respond. What we showed, through a series of in vitro experiments in which we mixed cells of different types, was that the same group of patients who did not respond to mitogen also had, in their peripheral blood, highly suppressive cells. What I'd like to think now is that those cells are the same autoreactive cells that are the result of the antigen-nonspecific pathway, that when a B cell interacts with antigens or mitogens in the gastrointestinal tract, an autoreactive cell is produced and becomes a suppressor cell—the cell that we were finding in our in vitro system. So in Crohn's disease these suppressor cells are a footprint of ongoing cell activation, probably cell activation, by antigen.

To try to prove that, we moved to the study of primates, in particular the cynomolgus monkey. Infecting those monkeys with a self-limited infection with the lymphogranuloma venereum strain of *Chlamydia trachomatis* caused in the rectum a little aphthous ulcer over a lymphoid nodule, histologically the same kind of lesion that one finds in early Crohn's disease. We found that two weeks after infection, a wave of antigen-nonspecific suppressor cells appeared in the peripheral blood—not in the rectum, and not in the gut wall itself. In early Crohn's disease, these antigen-nonspecific suppressor cells are also found.

This allows us to begin to say something about the pathogenesis of Crohn's disease. What I think is that either one antigen, or perhaps a set of antigens, are stimulating the system, the helper cells, the B cells; and, in stimulating B cells, they activate B cells and give rise to the antigen-nonspecific suppressor cells which have some feedback suppressor effects. This cell, then, is holding back the disease. It is decreasing the excess response, because the excess response resides in an excessiveness of either the helper-cell response or a failure of the antigen-specific response. This cascade of suppressor cells, which are antigen-specific suppressor cells, is what is primarily necessary to control response. So one can suppose that these antigen-specific suppressor cells are not working in Crohn's disease, are not turning off the response of the helper and the B cell to antigen, and the only negative feedback regulation is through the antigen-nonspecific autoreactive suppressor cell which is present in the early stages of the disease. It is not present in later stages because this system becomes exhausted. So one can think of Crohn's disease as an excessive response due to a failure of the antigen-specific suppressor-cell cascade. The system makes a feeble attempt to compensate through the antigen-nonspecific suppressor cells, but the attempt is inadequate, there is an overexuberant response to common antigens, and the disease occurs.

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Gastroenterology in the United States, 1935–1985

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The first half of the 1980s was a period of tremendous adjustment and changes in our medical (or quasisurgical?) specialty. It seemed perfectly natural that we should accept each new advance unhesitatingly and eagerly. We don't seem to have had any future shock in gastroenterology, perhaps because advances in our field lagged so far behind advances in the other specialties that we were prepared. Like a bacterial culture, we were about to enter a log phase of growth. Since I am neither a professional historian nor a sociologist of medicine, my account of the first 50 years of modern gastroenterology must perforce be a personal narrative.

In the 1930s. In the United States, gastroenterology in the 1930s was the creation of a handful of men and one woman. In physiology, Cannon was studying motility in the goose using x-rays, with bismuth as the contrast medium. Carlson was continuing the work that William Beaumont had begun a century before by studying gastric physiology in his famous fistula patient, and he himself swallowed a tube every morning to study his own gastric acidity. Ivy, in his research on gastrointestinal hormones, was discovering CCK. Walter Palmer was instilling acid into the stomach of ulcer patients and sometimes reproducing their pain, while Babkin in Canada was continuing the work of Pavlov and, in New York, Hollander was trying to demonstrate why the acid secreted by the parietal cell was 160 mEq/L. Philadelphia was the center of clinical gastroenterology in America. Bockus, at the University of Pennsylvania, was beginning to be Mr. Gastroenterology. Miller and Abbott were inventing their long tube and Ingelfinger of Boston was getting ready to go to Philadelphia to study the gut by way of tubes. In New York, Crohn and Winkelstein were writing on infections of the stomach, peptic esophagitis, describing regional enteritis, and measuring night secretions in ulcer patients. In Boston, Sarah Jordan at the Lahey Clinic was treating the irritable bowel syndrome with belladonna and phenobarbital, a formula still being used today. In Rochester, the Mayo Clinic was assembling a formidable team of clinicians and investigators. In the laboratory, Frank Mann was doing experiments on the critical role of the liver by performing total hepatectomy in dogs. Jessie Bollman was studying the flow of lymph from the liver to understand ascites and cirrhosis. Bargen was wrestling with ulcerative colitis and separating out Crohn's disease; indeed, we think in retrospect the same patients were traveling between New York and Rochester getting a second opinion. Bargen suggested to my colleagues at Mount Sinai that they not call this disease "terminal ileitis" (the title of the paper they gave at the AMA in 1932)—Bargen thought the patients would draw the inevitable conclusion that they had a terminal disease—and my colleagues were smart enough to follow Bargen's advice. A group of clinicians around the country was trying to elevate the levels of standards in gastroenterology as an emerging discipline; among surgeons who were setting the stage were Elman in St. Louis, Dragstedt in Chicago, and Wangensteen in Minneapolis.

In the 1940s. To know where we are now and where we should go in the future, we need to know where we started. For me it began in the

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fall of 1939 when I, a frightened intern, went out on the wards at Mount Sinai Hospital. What was available as we all faced the patients sick with gastrointestinal problems?

History. History taking was certainly the most important of our diagnostic resources. If the patient had lost her appetite and couldn't eat (especially meat), we thought of cancer of the stomach; if he had lost his taste for tobacco, we thought of liver disease. We were concerned about the amount of alcohol he drank but we didn't fuss over how many cigarettes she smoked. If he complained of abdominal pain, we spent a lot of time trying to decipher the pattern of pain and relief from food and deciding whether an ulcer was gastric or duodenal; this exercise made us feel like sophisticated clinicians. If the patient complained of diarrhea, we wanted to know if he had been abroad, especially in the tropics; if he bled, we were interested in the color of his stools; if he didn't bleed, we were concerned with stool content and odor. We looked for white blood cells in the smears and especially eosinophils. We thought these were very important in inflammatory bowel disease.

Family history seemed to be very important, as cancer ran in families and women had family histories of gallstones. We thought about the pancreas and we wanted to know about alcohol intake. Cancer of the pancreas was so rare that it was presented at Grand Rounds. Diarrhea with fever and blood meant enteric infections, perhaps the dreaded disease ulcerative colitis. Crohn, Oppenheimer, and Ginsburg were instructing us to look out for diarrhea in young Jewish college students complaining of weight loss.

Physical Examination. In spite of what has been written, the physical examination was not quite as important as you might think from the anecdotes of my colleagues. Looking for jaundice by the window and not by yellow electric light was the burden of the house physician. He spent a lot of time feeling for the spleen, percussing the size of the liver, and looking for the stigmata of liver disease. All gastrointestinal consultants knew it was their duty to do a rectal examination and to console the family. Now, of course, we still do the rectal examination, but we feel it is the patients we must console.

Other Diagnostic Procedures. Blood counts and careful blood smears were usually the first step. Rigid sigmoidoscopy, after careful cleansing, was done by the senior attending on the medical service. Gastrointestinal radiology was well developed. Templeton in Chicago had worked out the nuances of mucosal patterns; the small bowel was still in "no man's land" and in the original paper on regional enteritis, no radiographs (and no photomicrographs) were reproduced. Barium enemas were easily available, and they were helpful. If we wanted to fish out a foreign body from the esophagus or biopsy a lesion, we called the nose and throat department for rigid endoscopy and we knew the risks of perforation.

We had crude methods for detecting gastric and esophageal function. For esophageal swallow, I remember, we would give the patient a drink of water and listen to the epigastrium to see how long it took for the fluid to reach the stomach; to measure delays in gastric emptying, we aspirated the stomach in the morning to see if we could recognize prunes fed the night before. We spent a lot of time doing gastric test meals, thinking they were important in separating gastric ulcers, duodenal ulcers, and gastric cancers. Our test meals were alcohol or gruel; we did not realize how little of a stimulus these substances were for acid secretion. A few hardy souls had mastered the semirigid gastroscope which Schindler brought over from Europe when he left there to avoid the tyrants. We tackled gallbladder disease with the Graham test, avoiding the trap of removing the gallbladder if it failed to visualize on a single dose of dye. We felt we were very hot then. If the x-rays were negative, we could rely on Lyon's duodenal aspiration, looking for cholesterol crystals; the circle has come around again because that is what we are doing today if the x-rays, the sonogram, the ERCP and the CAT scan are negative. If the patient was jaundiced, we watched him for three weeks and if he didn't get any better, we would do an exploratory procedure. In the meantime, we amused ourselves by trying to separate intrahepatic from extrahepatic obstruction by feeling for the gallbladder; we looked for urobilinogen in the urine and we relied on the cephalin flocculation as a test of liver function. We didn't think it was a bad mark on our escutcheon if we resorted to explorative surgery; we often did, to find out if we could cut out anything that was causing the pain or weight loss.

As for pancreatic disease, we relied on blood sugar and serum amylase. Elman in St. Louis had been beating the drums for that. Flat plates were obtained, looking for calcifications. A lot of ingenuity was applied to describing the duodenal sweep with air insufflation or the use of anticholinergics to induce hypotonia in the duodenal loop. We looked at the stools for fat and we smeared them and stained them with Sudan red. We didn't strain the stools for biliary calculi, but we knew that abroad they were finding that a help in the diagnosis of biliary-tract-associated pancreatitis.

Treatment. With these diagnostic tools, we could not do very much for our patients. I remember Leon Ginsburg telling me that graduating as a house physician at Mount Sinai in 1925 armed with digitalis, iron, quinine, insulin, alkaline powders, and aspirin, he turned around and went through the house again to train to be a surgeon. He felt that as a surgeon, he could at least cut out some of the patient's troubles.

When I entered the wards, we had a good blood bank. I had done my last direct blood transfusion of citrated blood from relative to patient as an extern during my sophomore summer; nowadays some of our patients in New York are very anxious to go back to direct transfusions from their relatives to avoid AIDS. Sulfanilamide was around; the latest antibiotic was sulfapyridine, which was very effective against the pneumococcus in toxic patients and was to resurface as the toxic half of sulfasalazine. I can still remember the cyanosis it caused in these already anoxic pneumonia patients. For difficulties in swallowing, the nose and throat department would dilate the esophagus by slipping a wire down through the rigid scope. The more adventurous senior attendings in gastroenterology dilated the esophagus with graduated rubber tubes. For intestinal obstruction, we had Wangensteen suction and the Kantor long tube. We gave intravenous fluid safely, but we had trouble getting sodium and potassium in an emergency; they usually took a few days. We treated ulcer patients with Sippy's program, milk and alkaline powders, mostly sodium bicarbonate and calcium carbonate. Winkelstein thought he was advanced in the field when he insisted that we treat our patients with nasogastric drips of alkali and milk during the night, and we usually had a lot of trouble because this mixture clogged up the tubes.

For gallstones and common duct stones, we explored our patients. If bleeding from duodenal and gastric ulcers did not stop promptly, we operated. For duodenal ulcer we were doing subtotal gastrectomy. We were pretty well convinced that the standard operation in America at that time (gastroenterostomy) was a failure. One surgeon at Mount Sinai used to cut one of the vagus nerves, but that didn't seem to help; we were all chagrined and a bit envious when only a few years later Dragstedt said we ought to cut both vagi. For variceal bleeding and liver disease we could do little except transfuse the patient and tap the abdomen for ascites. For cancer of the stomach we cut the lesion out. In cancer of the pancreas, we were under the spell of Whipple (who was up the street at Columbia) and we cut out everything in sight. Cancer of the colon was easy; sigmoid colostomy for cancer of the rectum was a reasonable way of life. For Crohn's disease of the ileum, we would resect in one or two stages, and sometimes we stopped after the first stage because the patient felt so much better; we often did a bypass which later we were to rue, as we still do today. For ulcerative colitis all we had was intravenous fluids and small blood transfusions; many times we did a diverting ileostomy only to find that it didn't help. Sometimes we shocked our patients with an *Escherichia coli* antiserum; I am sure this treatment simply released ACTH and cortisone. We did subtotal colectomies for ulcerative colitis to avoid the trauma of perineal resection, in the vain hope that we could later reanastomose the bowel; at least we held that hope out to our patients. Sometimes the colectomy was successful, undoubtedly because the patient had Crohn's disease.

Landmarks 1935–1985

Against this background of unbelievably primitive modalities of study and treatment, I sketch what I think have been the most important landmarks in gastroenterology. The efflorescence of gastroenterology was (and for me continues to be) a thrilling experience. Newton said that he had made so many discoveries because he felt like a child walking along the beach picking up pebbles. Just so, almost anybody who made any observations about the gastrointestinal tract between 1938 and 1985 on any scientific level could find out something new about its function and its diseases.

If a clinician who died in 1935 were to be revived today, the most striking change would, I think, be the emergence of gastroenterology as a strong specialty. When I was at Columbia, Robert Loeb was the dean of American eastern seacoast professors of medicine. He said a gastroenterologist is a man who wears a pince-nez with a black ribbon around his neck and is saving up money to buy a gastroscope. When Alexander Gutman came to Sinai from Columbia in the 1950s to chair the department of medicine, he knew no gastroenterology because there was none at Columbia.

Organizations and Publications. The American Gastroenterological Association, the New York Gastroenterological Society, the American College of Gastroenterology, the Gut Clubs, and the whole apparatus of gastroenterology have produced great changes in the last 50 years. I am a vanishing species of gastroenterologist—one who never belonged to a training program. The NIH grants for graduate training programs in gastroenterology made all the difference in formalizing clinical training.

In 1935 there was one journal, the *American Journal of Digestive Disease and Nutrition,* which was the official journal of the American Gastroenterological Association but the private property of Beaumont Cornell, who practiced in Elkington, Indiana. The AGA couldn't buy it from him, so in the 1940s formed the journal *Gastroenterology.* Neither that journal nor the others—*Gut, Journal of Clinical Gastroenterology, American Journal of Gastroenterology, Scandinavian Journal of Gastroenterology*—have been around forever, nor have the serial publications.

As for textbooks, Crohn's *The Affections of the Stomach* was a big, fat book, one of the few available, which I myself never read. Bockus made the first great impact with his books, joined later by Spiro and by Sleisinger-Fordtran. (I leave aside the whole world of liver disease, of which I have no firsthand experience.)

Physiology. Another emergence was the Age of Physiology; anyone could make a discovery in the physiology of the gut because it was all still to be done. As I think about the important contributions proceeding down the gut, I am sure that people were doing esophageal manometry before Code, but Code and his group at the Mayo Clinic were the real innovators. His atlas made us all feel that there ought to be somebody in each of our hospitals who could do esophageal manometry. The whole field of gastric secretions blossomed forth. We knew that Edkins thought he had proved the existence of the gastric secretory hormone, but he had been vigorously repudiated by all the leading gastrointestinal physiologists of the early twentieth century. He had resigned his chair in physiology and became depressed; I don't think he committed suicide, but he certainly had given up the thought that gastrin existed. Yet suddenly Gregory had isolated the hormone from the antrum and synthesized it and had shown that it had physiological activity. The small bowel had been in no man's land; but now everybody was passing a tube down. Fordtran and a hundred other people were perfusing the small bowel and were studying isolated loops in determining the mechanisms involved in intestinal absorption of water and electrolytes. We looked forward each week to a new paper that would tell us, for example, about the intricate mechanisms of the absorption of vitamin B-12. The journals were filled with an endless debate about where fat was absorbed. A lot of ingenuity was expended on electron microscopy on stained sections of the bowel to attempt to determine whether the fact that you didn't see fat in the ileum and jejunum meant that it was absorbed or wasn't absorbed there, until it became clear from perfusion studies that it was the ileum that was absorbing bile salts and that they were necessary for fats to be absorbed in the upper small bowel.

People were working very hard on the endocrine and exocrine pancreas.

Taking their cue from studies of motility of the esophagus, pediatricians were telling us we ought to study motility of the rectum and anus as well. We might even be able to find forms of Hirschsprung's disease in adults; here I think the work of Schuster in Baltimore was very important in studying colonic function.

Then there was that tremendous outburst, the hormonal explosion. Part of it was related to the development of the radioimmunoassay, but in addition the classical methods of endocrinology now returned to gastroenterology. After all, the first hormone to be discovered was secretin. Gastroenterologists had lost their hold or interest in the field of endocrinology and once again they were back with gastrin, secretin, and CCK; then there was an interesting problem with cholecystokinin and pancreozymin. Were they the same hormones or not? Harper had made his reputation and gotten his chair because he found a hormone that caused the pancreas to secrete enzymes, and Ivy and his colleagues had said that CCK acted only on the gallbladder; then it became clear, when the hormones were synthesized, that they were the same.

Functional Testing. While these physiological discoveries were being made we were immediately trying to apply them to functional tests of our patients. We thought that Lionel Bernstein had made a great advance when he began to perfuse the esophagus with acid and tell us whether patients had esophagitis. I alluded earlier to Palmer's test in the diagnosis of ulcer disease; now we were paying a lot of attention to perfusing the esophagus with acid to demonstrate the presence of esophagitis. We were not in the flexible fiberoptic system yet.

We were all pleased with two surgeons who discovered that some tumors of the pancreas caused gastric hypersecretion and soon we began to do basal and maximal acid secretions and we got excited over the fact that we could now separate some patients with what we used to call malignant ulcer disease. We didn't have the slightest understanding of what was going on but we would sign them out as "malignant ulcers." If they didn't have cancer they might as well have had, because every operation we did short of total gastrectomy seemed to lead to recurrence of ulcerations.

Since we knew that different hormones caused the pancreas to act in different ways we began to follow up the leads begun in Sweden and do pancreatic function tests by actually aspirating the duodenal secretions; at the same time as the physiologists were telling us about the enzymes involved in small-bowel dysfunction, we began to do tests of small-bowel function, D-xylose, lactose tolerance, and fecal fats. Technicians had to be paid a little extra to do 72-hour fecal fat determinations, but at least we could get them.

Even before the advent of flexible endoscopy, the impact of biopsy of the intestinal tract on our understanding is now unimaginable. We envied the liver and the kidney people because they could do biopsies. The evolution of the biopsy of the small bowel began with Wood, in Melbourne, doing blind biopsies of the stomach in an attempt to study gastritis. Margot Shiner had the simple but perfect idea of taking Wood's tube and shoving it down into the duodenum to come up with fragments of duodenal (and possibly on occasion jejunal) mucosa. A controversy had been raging in the literature over whether the changes in the small intestine in sprue were artefacts of the postmortem examination. Hess-Thaysen, the Pope of sprue in Sweden, had taken the view that all the changes in specimens discovered at operation or in cadavers were artefactual. Margot Shiner showed that if you pushed the Wood's tube down a little farther, you could get a biopsy that showed villous atrophy. Almost at the same time, Crosby described his capsule; a little bit later, Cy Rubin came forth with his multiple hydraulic system getting multiple biopsies. Each of these advances, now taken for granted, was a revelation to us. Then, with the development of the fiberoptic system, when biopsies became so much easier and one could have a targeted biopsy instead of a blind one, the whole concept of premalignant lesions at both ends of the gut took a dramatic and interesting turn.

People are always talking about the war on cancer and "targeted research." (Wouldn't it be great if we could make the body transparent! How would one go about getting a grant from the NIH to solve that particular problem in advance today?) It was by accident that Roentgen observed, when he was studying high-energy physics, that he could take an x-ray. We have to allow for chance in a prepared mind in research; I personally feel that not too much has come out of targeted research, at least in the gut. Certainly I think the important advance in imaging even before fiberoptics was the image intensifier. Radiologists used to walk around with those red glasses for up to 30 minutes to adapt to the dark. The scans of liver and spleen, to say nothing of the more recently developed technologies of CAT scan and sonography, were marvelous advances. Angiography, as far as I am concerned, plays its major role in the management of bleeding. Development of chromium labeling of red blood cell is also an important advance.

Pathophysiology. Paralleling the development of technology and physiology, American gastroenterology focused on pathophysiology; that was the hallmark of the day. Through endoscopy and biopsy, the concept of aganglionic disease emerged during this period. Following the contribution of Zollinger and Ellison that led to the discovery of the hypergastrinemic states, we spent a lot of time worrying about a retained antrum in postoperative patients with recurrent ulcers. It was when Berson and Yalow developed the radioimmunoassay that the entire area was clarified.

Management. Another point of interest to me is that great progress in the surgical and medical management of ulcer disease occurred during this period. Our operations became less gross, and we removed less tissue. We moved from subtotal gastrectomy to selective and superselective vagotomy. At about the same time, the number of patients with ulcer disease began to decline. Stimulated by the results of studies on gastric physiology and hormone secretion, we began to refine our approach to the inhibition of acid by more specific attacks at the cellular level. We had had atropine for a long time; then in the early 1950s probanthine and the other synthetic anticholinergics held the scene. I was disappointed with my observation that acetazolamide, which inhibited acid secretion in the stomach by blocking carbonic anhydrase, also inhibited carbonic anhydrase everywhere else in the body, and thus didn't seem to be a reasonable way of attacking ulcer disease. Then came the H2 blockers and their elucidation and refinement, and most recently, the proton pump inhibitors. Now that we can abolish acid secretion entirely, we are starting to worry about the possible later development of gastric cancer. As one who has used only a rigid sigmoidoscope, I see flexible endoscopy as obviously useful; it has also opened up the field of premalignant lesions: Barrett's esophagus, the stomach in pernicious anemia, gastric atrophy and polyps, adenomatous polyps and colon dysplasia.

Water Is the Last Thing a Fish Notices. Now for some things we all take for granted that were developed during the past fifty years (as someone said, water is the last thing a fish would discover). The most important is the development of antibiotics, especially their use to control surgical infections. How ironic that we now have a new class of gastrointestinal diseases caused by some of these antibiotics! In inflammatory bowel disease, we had transfusions, intravenous fluids, or ileostomy and subtotal colectomy. It was only about 1957 that steroid treatment was reported. Equally important was the surgical refinement of the Brooke ileostomy.

Conceptual advances in physiological methods for studying the gut have also been important. What a revelation to be able to separate diarrhea into two groups, osmotic and secretory. Fordtran crystalized previous physiologic work into a simple but strong idea: If a patient's diarrhea ceased when he was not fed, we were on the osmotic track; if it persisted, we had to look for secretory stimuli. This was a major conceptual advance.

Clinical trials are a boon. It is true that we didn't need many such trials to prove that penicillin was beneficial in pneumococcal pneumonia, but we had to see if what we had been doing by rote was beneficial. We all knew that antacids helped ulcer patients, but now we really know that they do. Not only the medical trials of treatment with antacids, H2 blockers, and prostaglandin analogs, but also the contemporaneous surgical controlled trials helped to settle some of the polemics about the best treatment for duodenal ulcer. A lot of our rituals for the treatment of acute pancreatitis (nasogastric intubation, Trasylol, peritoneal lavage) turned out not to be effective, but at least we cleared the air of the verbiage and the rituals we had carried out for years. In inflammatory bowel disease we are beginning now to have really good controlled trials. Thus, clinical trials were and are a tremendous conceptual advance. Another simple concept, the actuarial method of life tables, has changed the GI literature dramatically.

Other conceptual advances arose when someone asked simple but relevant questions. One of the best examples is Mike Levitt's contribution to "What is gas?"—a centuries-old complaint that we all knew about but could not answer. Levitt undertook, I think under Doctor Ingelfinger's prodding, to find out whether patients complaining of gas really had more gas.

I can't remember where we got that very handy label, "irritable bowel syndrome," that enabled us to feel comfortable dealing with a real entity (we know that 40% of all patients who come to see us have functional bowel syndromes). I think Almy and his colleagues pioneered in helping us define these patients. Since then everybody has attempted, with cluster analysis, to define more closely the concept of the irritable bowel, but the label itself was a marvelous conceptual advance: some of the patients we were operating on for intestinal obstruction really didn't have obstruction at all, but some neurogenic dysfunction that mimicked it. I think it is too bad that Snape and Cohen's work hasn't turned out to be correct, but I certainly think we are going to find that the irritable bowel is some dysrhythmia of the colon or the small bowel.

The Next Fifty Years

I think it was Sam Goldwyn who said, "Never prophesy, especially about the future." However, on certain technical predictions we are on good ground. We are going to have endoscopic visualization of the entire small bowel, and I am impatiently awaiting this. We are going to have biochemical scanning especially of the pancreas, fully developed automatization enzymology of small-bowel biopsies, and bedside methods for reporting pressure and absorption and visualizing motor events. We are going to have some methods for measuring blood flow to help us in some of the obscure syndromes undoubtedly related to vascular phenomena in the gut. All the gastrointestinal hormones will be measured easily, including those present both in the brain and the gut.

Predicting conceptual advances is hard. But I think somehow we are going to end up having syndromes of sick sinus or sick pacemaker functions in the gut; hints of it have already surfaced. I prophesy also that we will see the return of those interested in the liver and the gut into one big organization. Therapeutically, we are going to see better and safer chemical dissolution of gallstones, drugs to increase the resistance of the duodenum to ulcer disease, and more specific drugs for inflammatory bowel disease. We are going to have some way of getting the past drug history of our patients on the screen when they call us on the phone so we don't prescribe the drug which last time caused them to break out in a rash. That slow virus that is the cause of Crohn's disease is going to be isolated. And the gut will be the last organ to be transplanted.

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Immune Dysfunctions and Therapeutic Interventions in Patients with Acquired Immune Deficiency Syndrome and AIDS-Related Complex

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With the epidemic spread of the acquired immune deficiency syndrome (AIDS), scientific efforts to control this disease have become intense. The original perception was that AIDS would be confined to promiscuous homosexuals, intravenous drug users, Haitian immigrants in the United States and hemophiliacs (1, 2). It was proposed that an accumulation of assaults on the immune defenses leads to severe irreversible immunodeficiencies and multiple infections in the final stages (3–4). Following the identification of HIV (HTLV-III/LAV), a human T-lymphocyte retrovirus, as the infectious agent (5–7), a blood test that reveals antibodies to the virus was developed (8). Projections from recent epidemiologic data suggest that at least a million Americans have already been infected with this virus. Landesman (9) estimated that from 4% to 19% of those infected have developed AIDS during 1 to 4 years of follow-up and an additional 25% have AIDS-related complexes (ARC). These related syndromes, which include prodromal symptoms such as malaise, weight loss, lymphadenopathy, and lower ratios of T-helper (Th) to T-suppressor (Ts) cells (3, 4), have been observed not only in promiscuous homosexual men but also in women who have had frequent, diverse sexual contacts and no history of drug abuse (10, 11). These findings are consistent with sexual contact as the ultimate source of risk. They also suggest that the virus is capable of spreading to a section of the sexually active population larger than the four subgroups originally perceived as being at high risk.

Much has been learned about the immunologic mechanisms and natural history of AIDS and ARC. This article reviews current understanding and explores the phenotypic and functional abnormalities in persons with AIDS and with ARC, and therapeutic approaches to patients with ARC and AIDS.

Cellular Aberrations

T Lymphocytes. Our earliest immunologic findings in AIDS were phenotypic aberrations in both homosexual men with ARC and persons with AIDS. The mean ratio of T-helper and T-suppressor cells in these subjects were lower than in the heterosexual controls (12), a significant change caused by reduction in the number of helper cells in homosexual subjects at risk and in AIDS patients (Fig. 1); the number of Ts cells remained unchanged. In addition to this decrease in the number of total T-lymphocytes and T-helper cells, several defects in T-lymphocyte functions have also been observed. Both PHA and ConA-induced mitogenic responses are significantly reduced (Fig. 2), and the production of the T-cell lymphokine interleukin 2 (IL-2) is impaired (13). Antigen-specific primary cytotoxic T lymphocyte (CTL) responses, generally induced

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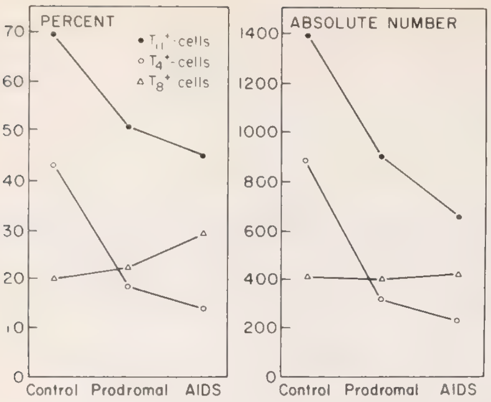


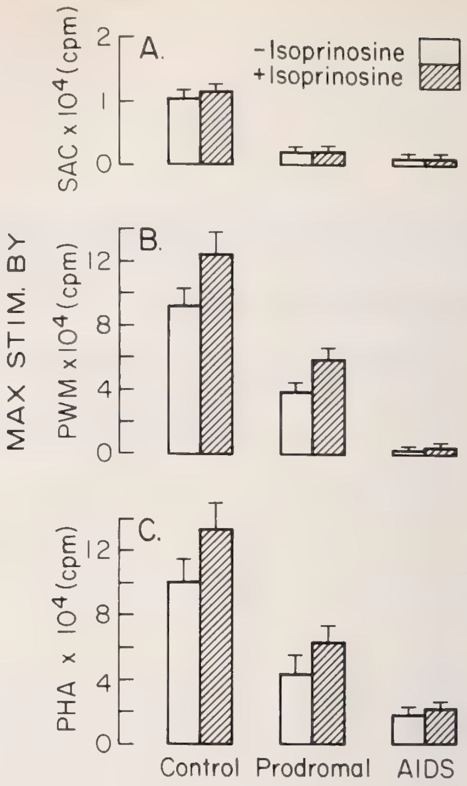
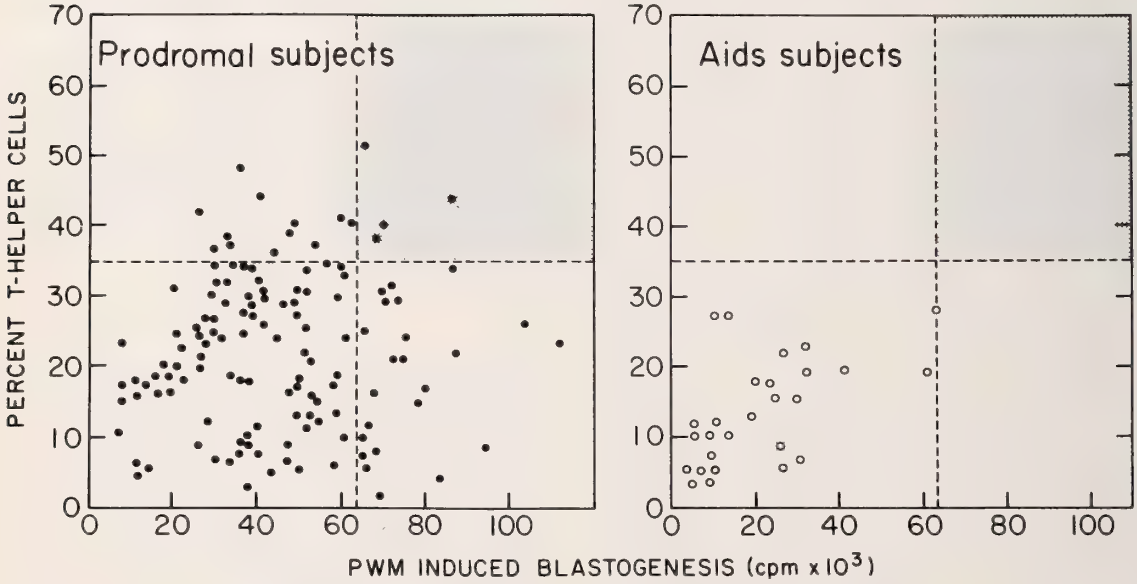


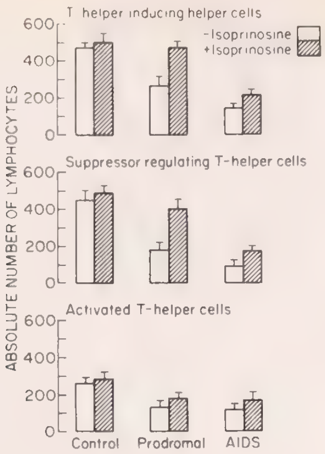
Fig. 1. Above Percentage and absolute number values for total T lymphocytes (T11$^+$ cells), T-helper cells (T4$^+$ cells), and T-suppressor cells (T8$^+$ cells), three subject groups.

Fig. 2. Right Functional aberrations and modulative effects of isoprinosine measured by blastogenic responses to three mitogens, AIDS and prodromal subjects.

Fig. 3. Below Association between marked decrease in helper T-cell numbers and impaired response to pokeweed mitogen (PWM) among prodromal homosexual males (●) and AIDS patients (○). Shaded areas: regions containing upper 95% of matched control group of heterosexual males with concurrent determinations on each parameter.



as a result of sequential interaction of helper T cells and IL2 with CTL precursors, were also significantly reduced (14). Furthermore, T helper cells have been shown to be particularly susceptible to the attack of HIV (HTLV-III/LAV). Klatzman (15) successfully interrupted viral replication in purified human lymphocytes by pretreating these cells with monoclonal antibodies to the Th antigens. McDougal (16) co-precipitated radiolabeled membrane particles from T helper inducer cells with a viral glycoprotein (GP110) isolated from HTLV-III and demonstrated that the Th molecule itself was the surface receptor to the virus. These recent reports support earlier hypotheses that quantitative and functional aberrations in T helper cells are instrumental in the immunoregulatory imbalance which prevails among AIDS patients and prodromal subjects.



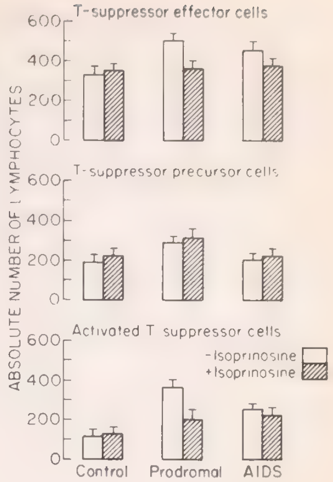


Fig. 4. **Left** Defects in helper cell subsets and modulative effects of isoprinosine.
Fig. 5. **Right** Defects in suppressor cell subsets and modulative effects of isoprinosine.

B Lymphocytes. We have also demonstrated an association between the marked decrease in T-helper lymphocyte numbers and the impaired response to T-cell-dependent B lymphocyte mitogen in AIDS and ARC subjects. Sixty-eight percent of the homosexuals with ARC and 95.7% of AIDS patients' helper T cells and pokeweed-mitogen (PWM)-induced blastogenesis were at or below the fifth percentile of the heterosexual group (Fig. 3). Similar comparison of T-helper cell number versus PHA-induced proliferation and T suppressor cell number versus blastogenic response to either mitogens failed to show this association (12). Concomitantly, a broad spectrum of aberrations in all stages of B cell development were observed. Failure of isolated PBL from these subjects to respond to the polyclonal B-cell activator SAC indicated intrinsic defects in their resting B cells; impairment in PWM-induced blastogenesis coupled with increased levels of Ig secretion signified regulatory defects in their mature B cells that may be related to helper suppressor dysfunctions (17).

NK Cells. Defects in NK cell and monocyte functions have also been described. Although the number of Leu7+ (18) or Leu11$^+$ (19) NK cells in AIDS patients did not differ significantly from that of normals, significantly lower NK-cell-mediated cytotoxicity was observed compared to that in normals, suggesting that NK cells in these patients are less active. In a study of male homosexuals at risk, we have reported heterogeneous NK function which appeared virtually unrelated to the total number of circulating NK cells (Table). Twenty-six percent of the homosexual participants had NK activity significantly lower than that of the heterosexual controls but similar to that observed in the clinically confirmed AIDS patients. A uniform lack of response to IFN and IL2 modulation was also demonstrated in this low-NK group (18).

Monocytes. In addition to these impairments in T cells, B cells, and NK cell functions, adherent mononuclear cells in AIDS patients were also found to be defective. Shannon et al (19) reported that the addition of autologous monocytes to highly purified T cells of AIDS patients elicited poorer proliferative response to pokeweed mitogens than in normal controls. Monocytes of AIDS patients were also poor producers of Il-1 in vitro (20). Our findings as well as those of other investigators indicate that the mechanism of cellular dysfunction in AIDS is multifactorial and may involve defects in leukocyte populations in addition to the decrease in T-helper lymphocytes. These observations also reveal several contradictions when one correlates the functional deficiencies of persons with AIDS and prodromal subjects with their cell surface phenotypes. Despite profound depression in Th cells, immunoglobulin levels in both prodromal subjects and

TABLE
Natural Killer Cell Activity in Prodromal and AIDS Subjects

Study groups	NK-cell activity %		
	Alone	+IFN	+IL2
Control heterosexual	21.7	31.8	30.0
Prodromal subjects			
Normal NK function (34%)	23.0	27.2	21.5*
Heightened NK function (40%)	29.1	13.3*	15.3*
Low NK function (26%)	7.8*	8.5*	9.4*
AIDS patients	8.4*	6.0*	9.5*

* $p < .001$ compared to control heterosexual.

AIDS patients are elevated (21, 22). Although B cells are present in normal number and the in vivo Ig levels are high, B-cell function as reflected by proliferative responses to both T-cell-dependent (PWM) and T-cell-independent (SAC) mitogens is depressed (12, 17). In addition, NK cell functions in these subjects appear unrelated to the total number of T-helper and suppressor cells and the circulating NK (Leu7+ or Leu11$^+$) cells (18). These controversies demonstrate that it may be inappropriate to equate the expression of Th and Ts cell surface antigens with specific functional properties and differential states of the cell.

Functional Subsets of Th and Ts cells. Recent developments of dual color flow cytometry and the availability of new monoclonal antibodies in characterizing and isolating T-cell subsets have provided a valuable tool for further elucidation of the cellular mechanisms involved in the immune dysfunctions in AIDS and ARC individuals. Simultaneously, two-color immunofluorescence allows quick and precise determination of lymphocyte phenotype, and series of monoclonal antibodies provide functional correlates within the Th and Ts subsets. Using FITC-conjugated Leu2 and Leu3 antigens and phycoerythrin-conjugated Leu8, Leu15, and HLA-DR (Ia) monoclonal antibodies, significant aberrations were observed by us on PWM-stimulated lymphocytes (Fig. 4). Among Leu3$^+$ cells, dual-color analysis demonstrated significant decreases in both regulator-helper (Leu3$^+$ Leu8$^+$) subset and inducer helper (Leu3+ Leu8$^-$) subset (23). The number of activated helper T cells (Leu3$^+$ HLA-DR$^+$) was not significantly affected in the peripheral blood leukocytes (PBL) of both AIDS and ARC patients. Among the T-suppressor (Leu2$^+$) subset of lymphocytes, we observed an increase in the effector Ts (Leu2$^+$ Leu8$^-$) and the activated Ts (Leu2$^+$ HLA-DR) subset for both study groups; Ts precursor (Leu2$^+$ Leu8$^+$) cells were within the normal range (Fig. 5).

The presence of HLA-DR antigen on Ts subsets distinguishes activated suppressor cells from cytotoxic T cells (24). These activated cells with the phenotype of Ts$^+$ Ia$^+$ are capable of producing suppressor-effector factors (such as TsF 120) responsible for both suppressing T-helper cell function and regulating the level of T suppressor inducer cell activity (24). These events define a feedback loop which regulates both the helper and suppressor T cell activities and B cell responses. Our results demonstrated that HLA-DR markers are abnormally expressed in AIDS and prodromal subjects and that the feedback regulatory pathway is defective. Based on these findings, it is proposed that the multicellular dysfunctions in AIDS involves defects in the feedback regulatory loops that modulate the helper and suppressor T cell system as well as NK cells and B-cell functions (23).

Immunologic Interventions in ARC and AIDS

Interferons. Current strategies in the therapeutic management of AIDS focus on treatment of Kaposi's sarcoma, on restoration of immunologic deficiencies in opportunistic infections, and on enhancement of natural resistance in prodromal individuals. For treatment of AIDS-associated Kaposi's sarcoma a variety of biological and chemical substances with immunorestorative potentials have been investigated. The first of these to enter clinical trials were cytokines such as the interferons and interleukin-2. Krown et al (25) demonstrated that recombinant leukocyte alpha interferon (IFN), when given in high doses, was able to induce regression of Kaposi's sarcoma in 8 of 35 patients tested. A similar response rate has been obtained in randomized studies by Volvending et al (26) and Groopman et al (27). No significant degree of protection against the opportunistic infections can be demonstrated, however, leading these workers to conclude that while alpha interferon can potentially be effective in the treatment of Kaposi's sarcoma, its therapeutic action may not involve immunologic augmentation. Clinical trials with other interferons have also been equivocal (28, 29).

Interleukin-2. In search of more effective treatment than interferons, many investigators have advocated the use of T-cell growth factor IL-2. In a number of in vitro studies, restoration of certain immune functions was demonstrated with lymphocytes from AIDS patients (30–32). Rook reported that the profound depression in NK activity in 6 AIDS patients he studied could be enhanced significantly by in vitro incubation with IL-2 but not with α-IFN (32). He also observed that IL-2 can normalize the decline in gamma IFN production in some AIDS patients (33). In light of these encouraging findings, a number of clinical trials have already begun. Lotz treated 5 patients with Kaposi's sarcoma but reported subjective improvement in only one (34). Lane treated 12 patients with this sarcoma and opportunistic infections and observed some decrease in total number of lymphocytes, with no change in Ts cells or NK and blastogenic activities (35). In a study using recombinant IL-2, Ernst et al (36) obtained transient improvements in all leukocyte subpopulations, and minor restoration of immune functions in 4 patients with AIDS and 3 with ARC.

Plasma Exchange. Since elevated levels of serum IgG and immune complexes are one of the most consistent immune aberrations in AIDS, their removal has been a subject of current investigations. Tamor (37) treated one AIDS patient with 3 courses of plasmapheresis and reported transient increase in the number of Th lymphocytes, which subsequently fell to baseline values within 2 weeks after therapy. Rubinstein et al (38) and Abrams et al (38) applied plasma exchanges 2 or 3 times a week for a period of 3 weeks observed some decreases in Ts cells, with transient increases in Th cells. Gupta (39) reported some restoration of suppressor T-cell functions in children with AIDS during intravenous gamma globulin treatments. Inada and Lange (38) treated 3 AIDS patients and observed some decreases in immune complexes as well as subjective improvement in symptoms. Although all these studies showed transient improvement in some parameters, the role of plasma exchange in AIDS is limited to adjuvant therapy only.

Chemotherapy. A variety of pharmacologic agents have been investigated for their ability to stimulate the depressed cell-mediated immunity in AIDS. Patt (40) treated 16 ARC patients with Azimexon (an Aziridine dye) and reported increases in lymphoproliferative response and delayed hypersensitivity as well as subjective clinical improvements. No such benefits were noted in 13 patients with AIDS treated by identical regimens. Fischl and Grieco (38) administered indomethacin, a prostaglandin inhibitor, on patients with opportunistic infections and ARC and observed transient increase in delayed hypersensitivity and decreases in diarrhea. Cimetidine, known to augment mitogen-induced proliferation in vitro, was reported by Grieco et al and Abrams et al (38) to induce no major immunologic changes. Rouvroy (39) used suramin, a potent inhibitor of HTLV-III reverse transcriptase (40), in ARC patients, and reported good clinical and immunologic improvements. There were, however, significant side effects, such as skin rash, fever, hepatitis, and nephritis. Other clinical trials of anti-HTLV-III replication reagents such as Ansamycin, Ribavirin, Foscarnet, and 3′ azido-3-deoxythymidine are still in the planning stage (41, 42).

Isoprinosine. Since 1983, we have investigated the in vitro effects of the immunopotentiating drug isoprinosine on both AIDS patients and homosexuals with ARC (2, 17, 43, 44). Our interest in this antiviral compound was stimulated by several earlier reports on its clinical and immunological properties. Hadden (45) and Wybran (46) were among the first to report that isoprinosine enhances mitogen-induced blastogenesis and stimulates normal human lymphocyte differentiation. Balestrin (47) observed in vitro augmentation of NK activity by isoprinosine in normal individuals to levels comparable to those obtained with IFN. Tsang and Fudenberg (48, 49) have reported enhancement of IL-2 production by isoprinosine and an increase in the number of IL-2 receptor-bearing lymphocytes (Tac + cells) in Con-A stimulated cultures of PBL from AIDS patients. Co-incubation with PBL from ARC patients has been observed by Pompidou to inhibit infection of lymphocytes by HTLV-III/LAV (50, 51).

Results from in vivo studies have also been encouraging. Isoprinosine has been shown to restore helper-T-cell functions of aged or irradiated subjects and to enhance contact sensitivity to picryl chloride (45, 50, 51). Its beneficial clinical effects on subacute sclerosing panencephalitis, acute encephalitis, and other viral infections have also been well documented (51, 52). In preliminary studies (12, 17) we have demonstrated that co-incubation with this agent potentiated T-lymphocyte functions of immunosuppressed subjects selectively. Among homosexuals with normal lymphocyte functions, the percentage of upward modulation for PWM-induced responses was comparable to that obtained in control heterosexuals. Among AIDS patients and ARC prodromal subjects a much higher degree of augmentation was achieved. In none of the tested subjects with severe immunodeficiencies, however, were the lymphocyte functions restored to the normal range established in the controls. As for B lymphocyte functions, isoprinosine had no modulative effect on the resting B cells (it did not enhance SAC-induced blastogenesis). It did, however, restore both T-cell-dependent PWM-induced transformation and the spontaneous secretion of Ig (Fig. 2).

These results suggested that isoprinosine may exert its regulatory influences through modulation of the helper and suppressor T cell functions (43, 44). To further elucidate this hypothesis, PBL from prodromal homosexuals and AIDS patients were analyzed following PWM blastogenesis by dual color flow cytometry using monoclonal antibodies that detect activated (HLA-DR) and functional (Leu8 and Leu15) subsets of the Ts and Th lymphocyte populations (44). Isoprinosine selectively modified the phenotypic co-expression of both HLA-DR and Leu8 antigens on helper and suppressor T cells (Figs. 4, 5). Among AIDS patients with severe immune dysfunctions, isoprinosine significantly reduced the elevated subset of suppressor-effector lymphocytes but exerted no actions on any other lymphocyte subsets. Among ARC homosexuals, co-incubation with isoprinosine augmented the expression of both the helper-regulating helper T cells and the suppressor-inducing helper T cells. The number of suppressor effector lymphocytes and activated suppressor cells were reduced (Fig. 4, 5). These interferences with the defective feedback regulation loop may explain the capacity of isoprinosine to restore, at least partially, the depressed cell-mediated immunity associated with AIDS. It also suggested a potential clinical use of this compound in the treatment of individuals and of patients with mild symptoms of AIDS.

In a double-blind placebo-controlled trial (53) we treated 61 immunosuppressed men who had persistent generalized lymphadenopathy with one of two doses (1 or 3 gm/day) of this drug or with a placebo for a period of 28 days. Clinical improvement was achieved in 11 of 21 patients in the high-dose group within 5 months of cessation of treatment, but in only 3 of 19 patients in the placebo group. The group of patients who received the higher dose of isoprinosine (3 gm/day) had dramatically enhanced NK cell activity by day 14; this elevation was still evident up to 1 year after treatment. An increase in total T and helper T cells which peaked 2 months after cessation of drug administration was also observed. The kinetics of these effects support the in vitro findings that isoprinosine stimulates the production of precursor T cells, thereby initiating a cascade of lymphocyte differentiation leading to partial restoration of cell-mediated immunity.

Our report of therapeutic efficacy of isoprinosine in immunodepressed ARC patients has subsequently been confirmed by other independent clinical trials. In a study of 76 patients with ARC, Corant observed significant changes in NK activity for up to 90 days, and in helper T lymphocytes by day 14. Starret, likewise, found greater increase in NK activity in an active treatment group of immunosuppressed homosexuals than in the placebo patients. Gupta et al, on the other hand, could find no changes in either the immunologic or clinical status of 3 patients with CDC-defined AIDS treated with isoprinosine (unpublished data on file, Newport Pharmaceuticals).

Summary

With the current expansion of knowledge of the etiology and cellular mechanism of AIDS, many immunotherapeutic strategies have been explored over the past couple of years. In vitro findings have been encouraging; mild or transient improvements have been recorded in clinical trials in some patients with mild symptoms or at early stages of the disease. Nevertheless, none of these modalities have had any significant effect in restoring T-cell-mediated immunity or in enhancing antibacterial or antiviral resistance in patients with severe opportunistic infections, nor have any of the modalities prevented the eventual evolution from ARC to AIDS. Public health measures such as changes in sexual practices and screening of blood products appear to have minimal impact in controlling the transmission of HTLV-III. Future work in elucidating the mechanism of viral interaction with immune system will, we all hope, lead to development of more effective therapeutic measures.

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Chlamydia trachomatis Infection in Sexually Abused Children

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Abstract

To determine whether the major route of infection with *Chlamydia trachomatis* in children is by sexual contact, we investigated the prevalence of chlamydial infections in 60 allegedly sexually abused children and compared that rate to the rate of *C. trachomatis* infection in 14 children with no prior evidence of sexual abuse. Thirty (50%) of the sexually abused children showed *C. trachomatis* infections. This was statistically higher than the rate (14%) of infection with *C. trachomatis* in the non-sexually abused group ($p < 0.05$). Furthermore, there was no evidence of *C. trachomatis* infection in the younger, under 13 years of age, controls, whereas, 43% of sexually abused children under 13 showed *C. trachomatis* infection. This difference was also statistically significant ($p < 0.05$). We conclude that the presence of *C. trachomatis* can be considered virtual proof of sexual contact. In addition, in children under 13, infection with *C. trachomatis* may be diagnostic and legally suggestive of sexual abuse. Furthermore, the level of *C. trachomatis* infection is high enough in sexually abused children to warrant routine *C. trachomatis* cultures of all cases of sexual abuse.

Chlamydia trachomatis appears to be the single most prevalent sexually transmitted disease (1–3). However, reports of *C. trachomatis* levels in adult women vary. Evidence of *C. trachomatis* infection was found in 4.6% of college women (4) and in 20%–30% of women attending sexually transmitted disease clinics (5, 6). *C. trachomatis* infections are also recognized as a major clinical problem in the neonatal period. *C. trachomatis* may represent the most common microorganism in neonatal ocular infections (7–9) and may be the cause of a large fraction of neonatal pneumonias (10).

Reports about *C. trachomatis*-related rectogenital infections in minors are less numerous. Golden et al (11) reported that 10.2% of sexually active adolescents between 12 and 17 years of age showed *C. trachomatis* infection of the endocervical canal.

Hammerschlag et al (12), in a study of 100 healthy girls, 2 months to 15 years of age, reported a positive *C. trachomatis* antibody in vaginal secretions of a 4-year-old asymptomatic girl and a 13-year-old girl with vaginal trichomoniasis. Neither had positive vaginal cultures, however. A positive vaginal *C. trachomatis* culture was obtained from another 4-year-old girl who had no clinical findings on examination. Paradise et al (13) identified no case of *C. trachomatis* in 35 premenarchal females with symptoms and signs of vulvovaginitis. In a matched control population, only 1 of 35 subjects cultured positive for *C. trachomatis*. Humoral antibodies to *C. trachomatis* in children have also been investigated. By demonstrating a progressive seropositivity with increasing age from 5% at 1–2 years of age to 7%–15% in 7–15-year-old children, San Joaquin et al (14) suggested that *C. trachomatis* infections occur commonly in children. Interestingly, no sex

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or race differences were observed; however, girls showed higher titers than boys. Similar data were obtained by Black et al (15), who, in addition to progressively increasing rates of seropositivity in both sexes, also reported a significantly higher seropositivity rate in female children aged 6–15 than in their male counterparts.

Some studies also attempted to investigate the level of chlamydial infection in sexually abused children. *C. trachomatis* coinfection was found in 33% of children with gonococcal infections (16). Ingram et al (17) and Hammerschlag et al (18) reported *C. trachomatis* infection rates of 4%–6% in sexually active and abused children. These rates, however, were not statistically higher than in control groups. Consequently, it has remained unclear whether *C. trachomatis* infections are associated with possible sexual abuse in children. Rettig suggested such an association, stating that genital infections with *C. trachomatis* in children are "statistically nonsignificant, but clinically important" (19).

This study was designed to gain a better understanding of the levels of *C. trachomatis* infection in children and adolescents with sexual contact. The prevalence of infections with *C. trachomatis* in allegedly sexually abused pediatric patients was investigated and compared to the rate of *C. trachomatis* infections in a control population of children with no prior evidence of sexual abuse.

Methods

Patient Population and Collection of Specimens. Mount Sinai Hospital Medical Center of Chicago serves a predominantly black and Hispanic, low-socioeconomic population on the southwest side of Chicago. Culture specimens of a "sexually abused" group of patients were obtained by the Department of Pediatrics as per protocol and referred to the Reproductive Microbiology Laboratory of the Department of Obstetrics and Gynecology. Cultures were obtained from the vagina/urethra, oral cavity, and rectum of 60 patients. In some instances, however, only specimens from the site of alleged sexual contact were obtained in order to minimize additional trauma to the young patient. This included 6 patients with genital specimens only, 2 patients with genital and rectal specimens, 1 patient with an oral specimen only, and 1 patient with a rectal specimen only.

The control group of 14 children included vaginal and urethral culture specimens from children referred to the laboratory from the pediatric department for workup of possible urogenital tract infections. All these children showed no evidence of child abuse after a detailed interview protocol was obtained.

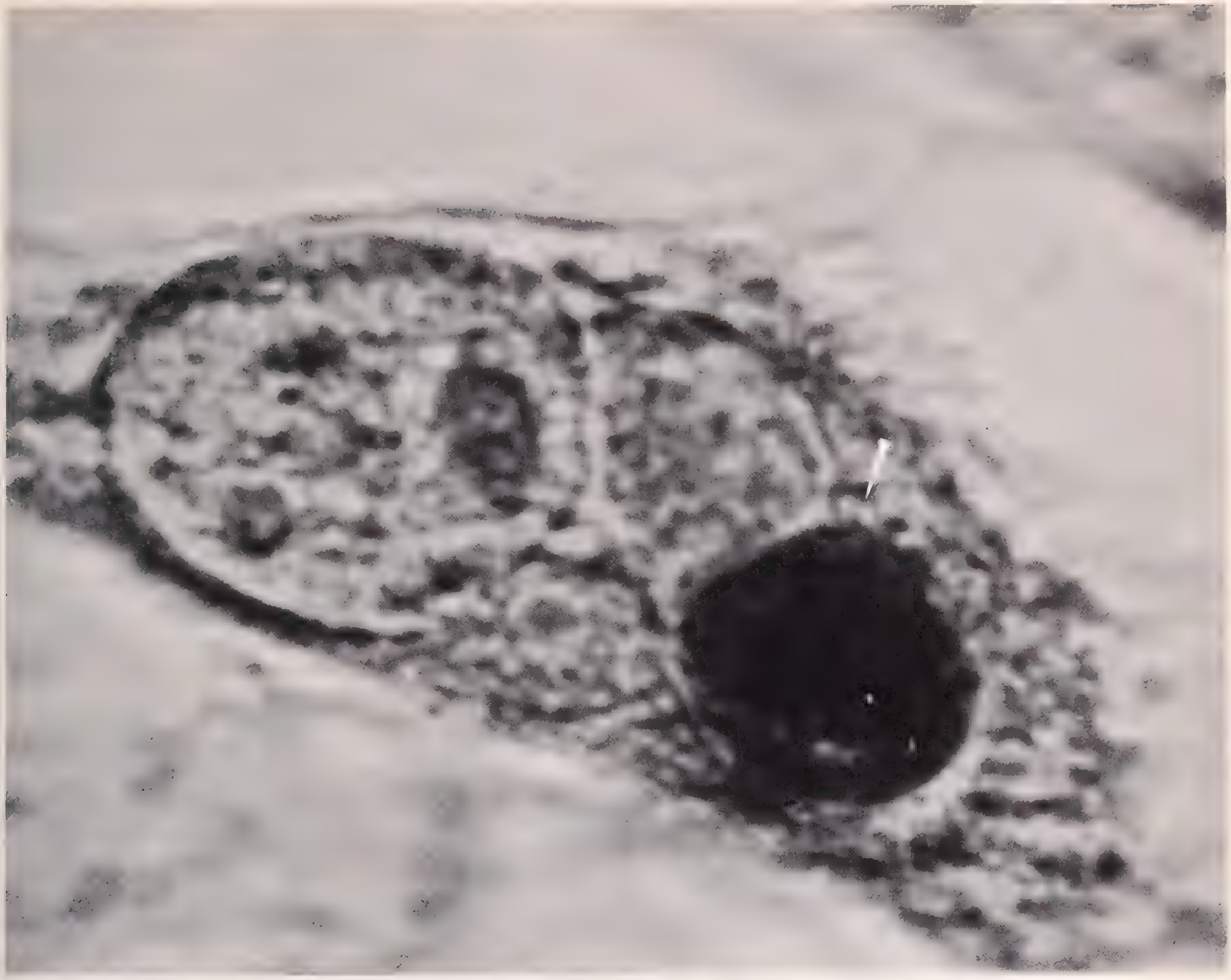
In all cases specimens were transported immediately to the Reproductive Microbiology Laboratory in a sucrose phosphate buffer (2SP). The tentative diagnoses of alleged sexual abuse or genital tract infection were made by the respective referring physician prior to the availability of culture results. In most cases diagnoses were, in fact, unknown to laboratory personnel until after culturing for *C. trachomatis* was completed. This study includes specimens obtained over a 1-year period starting June 1983.

Isolation and Detection of *Chlamydia*. *C. trachomatis* isolation was done on cycloheximide-treated McCoy cells grown on 12-mm cover slips in 15 × 45 mm vials. Prior to inoculation with specimen, the cells were treated with 1.0 ml of diethylaminoethyldextran (30 μg/ml, DEAE-D, Sigma Co.) for 30 min. The DEAE-D-pretreated McCoy cells were inoculated with 0.2 ml of transport media containing the specimen. The vials were then centrifuged for 1 hr at 500 g (Centra-7, IEC). The McCoy cells were then incubated at 37°C for 72 hr in minimal essential media (Flow Labs) modified with HEPES, gentamycin, and vancomycin.

C. trachomatis inclusions were detected using one or, frequently, two of the following methods. Originally, an iodine stain was used to evaluate cells for *C. trachomatis* inclusions. When staining with iodine, cultures were fixed by adding 1.0 ml of absolute methanol to the vials after aspiration of the culture media. After 10 min the methanol was aspirated and 0.5 ml of Jones' iodine solution was added. The iodine was aspirated after 10 min, and cover slips were mounted on slides with mounting media containing equal parts Jones' iodine solution and glycerol. Microscopic examination of each cover slip was performed at magnifications of 200× and 400× (Fig. 1).

Cultures to be stained with fluorescein-conjugated antibodies were fixed with methanol and then rinsed with deionized water. Fixed cultures were stained with 30 μl of fluorescein-conjugated antibodies in a solution containing Evans' blue counterstain (MicroTrak, *Chlamydia trachomatis* Culture Confirmation Test, Syva Co.). After 20–30 min, cover slips were rinsed with deionized water and removed from the vials with forceps. Cover slips were then mounted on slides and examined at 200×, 400×, and 1,000× for characteristic inclusions (Fig. 2).

Statistical Analysis. Statistical analysis of data



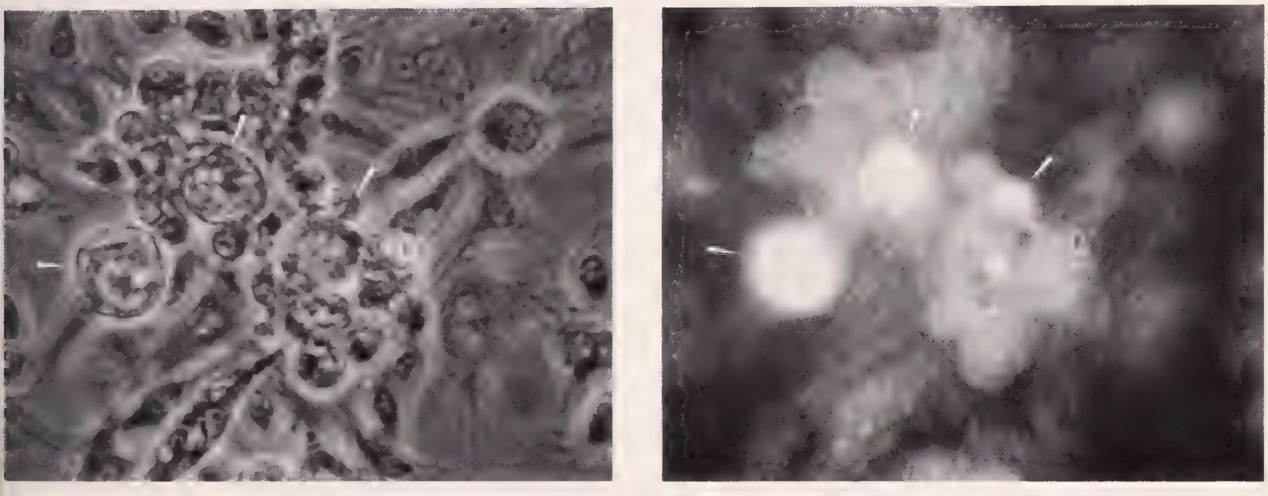


Fig. 1. Phase-contrast photomicrograph showing *Chlamydia* inclusion (arrow) in cultured McCoy cell (Jones' iodine, 1250×).
Fig. 2. Photomicrographs of cultured McCoy cells; arrows, cells with *Chlamydia* inclusions. **Bottom left** Phase contrast, 500×. **Bottom right** Fluorescence, 500×, same field; note large fluorescent inclusion bodies (arrows).

was accomplished using a standard chi-square test with a significance level of $p < 0.05$ and in confirmation, where applicable, Fisher's Exact Test.

Results

From June 1983 through May 1984, specimens from 60 pediatric patients who were alleg-

TABLE 1

Sex and Age Distribution of Allegedly Sexually Abused Children Screened for Chlamydial Infection

		Age	
	n	Range (months–years)	Mean ± SD (years)
Boys	13	12–18	7.1 ± 4.9
Girls	47	1–18	8.8 ± 5.2
Total	60	1–18	8.4 ± 5.1

TABLE 2

Site of Positive Chlamydia trachomatis *in Sexually Abused Pediatric Patients*

Site of positive cultures	No. of positive results
Vaginal/urethral	26*
Oral only	2
Rectal only	2

* Includes 16 patients with multiple-site infection.

TABLE 3

Prevalence of Chlamydial Infection in Sexually Abused and Non-sexually-Abused Pediatric Patients

	Age		
Abuse type	1 mon–12 yr	13 yr–18 yr	Total
Sexual	18/42 (43%)*	12/18 (67%)	30/60 (50%)
Nonsexual	0/7 (0%)	2/7 (29%)	2/14 (14%)
	$p < 0.05$	NS†	$p < 0.05$‡ $p < 0.033$§

* Number of positives/total number in group (percent positive).

† Not significant.

‡ Chi square.

§ Fisher's Exact Test.

edly sexually abused were received by the laboratory. Of these 60 patients, 42 (70%) were under 13 years of age (Table 1). The control group was 14 patients (male, $n = 2$; female, $n = 12$); 7 (50%) of the controls were under 13 years of age (age range, 2 months–18 years; mean, 9.2 years).

Of the 60 sexually abused patients, 30 (50%) showed positive *C. trachomatis* inclusions in specimens from either one or multiple sites. Twenty-six of these patients were positive at urogenital sites. Of these, 16 showed *C. trachomatis* infections at multiple sites, 11 at all three sites. Two patients showed *C. trachomatis* inclusions at oral sites alone, and an equal number only in the rectum (Table 2). The control group showed a statistically lower level of infection with *C. trachomatis* than the sexually abused group (Table 3; $p < 0.05$ (chi square) and $p < 0.033$ (Fisher's Exact Test). This significance level remains when considering only genital specimens.

Since adolescents are frequently sexually active, we further divided the groups according to age, below 13 years and 13–18 years, in an attempt to control for unreported sexual contact. In sexually abused patients, the adolescent group experienced a higher frequency of infection with *C. trachomatis* (Table 3) than children under 13 years of age (67% versus 43%). This difference, however, was not statistically significant. In the control group no *C. trachomatis* inclusions were found in specimens from children under the age of 13. Comparison of sexually abused children under 13 with non-sexually-abused children showed a statistically higher level of *C. trachomatis* infection in the abused group ($p < 0.05$). However, no statistically significant difference was observable in the adolescent age group.

Discussion

Consideration of sexually transmitted diseases and sexual abuse in children has increased greatly in the last decade. Kempe characterized sexual abuse as a "hidden pediatric problem" (20). However, until recently, little attention has been given to the sexual transmission of *C. trachomatis* in children. In fact, most studies showed a rather low frequency of chlamydial infections in sexually abused children, and failed to demonstrate a statistically significant increase of infection over control groups (17, 18). At least in some studies, however, the question is whether control children were in fact unexposed to previous sexual contact (19). The data reported herein stand in clear contrast to these previous reports. Furthermore, particularly for the age group below 13 years, the presence of *C. trachomatis* seems diagnostic of sexual contact or abuse.

The higher prevalence rates of *C. trachomatis* infections in this study of abused pediatric patients may stem from multiple factors. Methods for the isolation and detection of *C. trachomatis* utilized in this study differed from those of previous studies (11–18). In this study, polycation (DEAE-D) pretreated cells were utilized for culture. Evidence has been reported that pretreatment of cells with DEAE-D facilitates attachment and internalization of *C. trachomatis* (21, 22). We also utilized an immunofluorescent technique, only recently available commercially, which has been shown to be more sensitive than standard iodine stains (23). This increased sensitivity is due to the ability of the immunofluorescent technique to detect *C. trachomatis* at different stages of its life-cycle, whereas the iodine technique is positive only after glycogen deposits have formed around *C. trachomatis* inclusion bodies (24). Tam et al (25) recently reported yet another immunofluorescent technique with high sensitivity which allows culture-independent detection of *C. trachomatis*.

A second factor that may explain the high prevalence rates of *C. trachomatis* in our sexually abused children is the endemic level of chlamydial infections in the population served by the hospital. Preliminary results from incidence studies in the gynecologic and obstetrical population of the hospital suggest a higher incidence than reported from other U.S. centers for other female conditions such as pelvic inflammatory disease and even clinically fully asymptomatic states, as in the immediate postpartum period (Gleicher N, Suarez M, Friberg J, et al, unpublished data).

The difficulty in choosing a "normal" control group for studies of sexually abused children is apparent. It is ethically difficult to obtain cultures of genital organs from healthy children. The control group provided herein, although small, therefore seemed an ideal choice. It represents a closer approximation of "normal" than controls of some previously published studies (17, 18). Although patients in the control group were not healthy, as in some other reported studies (12, 14, 15), it appears that at least those children under 13 years had experienced no previous sexual contact. We also refrained from reclassifying allegedly abused children into the control group, as was done in other studies (17). Such a policy clearly contaminates the control group, since sexual abuse may be difficult to prove by history alone. This is particularly true for younger children (19, 20).

It has not been established that the major route of infection with *C. trachomatis* in children is by sexual contact. Such a contention is, however, supported by the total absence of *Chlamydia* infections in our young control patients under the age of 13 years, as well as very infrequent culture positivity in other reported series (12). Even the much less reliable serologic evaluations of young children indicate an increase of exposure to *C. trachomatis* with advancing age (14, 15). The presence of *C. trachomatis* in our young study population can thus be considered virtual proof of sexual contact. Our control population, on the other hand, although not completely healthy or asymptomatic, confirms the very low incidence of culture-positive *C. trachomatis* reported even in children with vulvovaginitis who are sexually inactive (13). Since *C. trachomatis* depends on the host cell as its total energy source, it is difficult to imagine *C. trachomatis* surviving outside a suitable host environment (26). From the data presented herein it therefore can be presumed that the presence of the organism may serve as a marker for sexual contact. In young children the presence of *C. trachomatis* has to be considered legally suggestive of sexual abuse. During the adolescent years *C. trachomatis* will be found at higher prevalence rates in sexually abused individuals; however, its presence cannot be considered diagnostic of sexual abuse. The incidence of *C. trachomatis* infection in allegedly sexually abused children is adequately high to recommend routine *C. trachomatis* cultures of multiple sites in all these cases.

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Abdominal Surgery in Elderly Patients: Statistical Analysis of Clinical Factors Prognostic of Mortality in 1,000 Cases

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Abstract

The high rates of abdominal disorders in a growing population of elderly patients and the greater willingness of the surgeon to cope with major problems in the elderly are factors contributing to a steady increase in abdominal procedures in this group.

The decision-making process in surgery for elderly persons is of great importance, requiring consideration of ethical, medicolegal, and economic factors in addition to the purely medical ones. One thousand consecutive abdominal surgical procedures in patients over 70 years of age were submitted to computer analysis, to determine the principal factors affecting mortality and morbidity. A high percentage of the procedures related to the biliary tract; the second largest group was for intestinal obstruction, both benign and malignant.

Analysis of data presented in this series leads to the following conclusions: (a) There is a declining mortality rate in elective operations in the elderly, in the absence of widespread malignancy. (b) The principal factors leading to high mortality in this series were age 80 and above, ASA category 3, inoperable malignancy, generalized peritonitis, and tumors of the pancreas. If two or more of these ominous factors are present, mortality above 50% is to be anticipated.

Modern medical technology has given us as physicians awesome powers. Our decisions not only affect the life and death of the individual, but also have a great influence over the rapidly increasing expenditures for health care delivery in most countries. In no area is the problem of such decisions as difficult as in surgery on older persons; dramatic surgical interference with the course of events for elderly patients affects us daily as clinical surgeons.

The central issue in every decision on whether to operate is a medical one: What are the changes of success in a given case? However, in practice, other issues that figure prominently (1) include the quality of life, both before and after surgery; the patient's ability to give informed consent; the surgeon's attitude and willingness to take risks; and economic considerations, such as expenses and availability of such special services as an intensive care unit.

Basic statistical data on old age have been presented by Comfort (2). These indicate, in essence, that if all known diseases could be cured, many more people would live to be 70 or 80, but very few would still be alive at the age of 90. His theories have so far been confirmed in that the percentage of people over 70 years is much higher in Western countries than in the Third World, whereas in both these areas only the same very small percentage live to be 90.

In fact, the percentage of elderly patients in the population of developed countries has increased from about 2% at the beginning of the century to between 4% and 6% now and is certain to reach 10% in certain countries by the end of the century. Furthermore, because of population

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TABLE 1
General Data

	Cases(%)
Sex	
Male	540(54)
Female	460(46)
Age group	
70–74	573(57)
75–79	264(27)
80–	163(16)
Procedure	
Elective	609(61)
Emergency	391(39)

TABLE 2
Vital System Involvement

	Cases(%)
System	
Cardiovascular	455(45)
Respiratory	139(14)
Renal	51(5)
Diabetes	123(12)
Miscellaneous	189(19)
ASA physical fitness class	
Category 1*	367(36)
Category 2†	468(47)
Category 3‡	165(17)

* Combines ASA 1–2: No clinically significant evidence of systemic disease.

† ASA 3: Moderate to severe systemic disease, not incapacitating, and no immediate threat to life.

‡ Combines ASA 4–5: Incapacitating systemic disease that is a constant threat to life.

TABLE 3
Major Diagnostic Groups, Benign Conditions

	Elective	Emergency	Total
Biliary tract	154	100	254
Peptic ulcer	42	65	107
Appendicitis	—	34	34
Mechanical obstr.	—	70	70
Misc.	26	56	82
Total no.	222	325	547
Total %	(40%)	(60%)	

trends in some cities, the percentage of old people in the population may approach 15% or more. These figures do not reflect the tremendous impact of the elderly on the medical system because of the high incidence of degenerative metabolic and neoplastic disorders in this age group. Among patients in a general hospital in our country, the elderly constitute 15.2%. Obviously, the elderly are heavily represented in certain types of surgical procedures, such as acute abdominal surgery, amputations of gangrenous legs, prostatectomies, and hip nailings (3–5).

Because of the frequent need for lengthy and costly rehabilitation of elderly patients, it is not surprising that in countries with comprehensive health insurance schemes, an estimated 24% of all health expenditures is related to the older segment of the population. As this percentage of the total expenditure increases, so may the pressure to limit, by legislation, the astronomical cost of optimal medical care for the aged.

As complicated as the issue of surgery for the elderly is, and as important as the role of the patient and the family may be, in the final analysis it is the opinion of the surgeon, based on experience, that will be the deciding factor in most cases. To formulate this decision with precision, knowledge of prognostic factors and estimated anticipated mortality are of great importance.

The purpose of this study is to try to create a system of estimating preoperatively the operative risk of mortality. Our computations are based on clinical factors that can be established easily and objectively before the operation. We chose this method rather than predicting prognosis on the basis of biochemical determinations, as was attempted in several previous studies.

Materials and Methods

In this series 1,000 consecutive major abdominal operations in patients over 70 years of age were included; minor procedures such as hernias were not. All patients underwent surgery at the surgical departments of Meir Hospital and Beilinson Medical Center between 1972 and 1982. Follow-up ranging from 6 months to 10 years was carefully maintained. Approximately 6% of the patients were lost to follow-up.

All data regarding the patients and their follow-up were recorded on a data sheet which included 72 items.

Certain basic rules which reflect our surgical philosophy were followed in this series. First, the preoperative period was used for intensive and rapid evaluation in all patients, with active participation of the anesthesia department. Modern techniques of diagnostic evaluation, namely ultrasound and fiberoptic endoscopy, were used early whenever needed (6). Second, early surgery, that is, surgery within 24 hr of admisson, was preferred whenever possible in acute and subacute situations. Also, whenever possible, definitive one-stage procedures were preferred and deliberate efforts were made to avoid gastrointestinal stomas, whether temporary or permanent. Finally, monitoring equipment was fully utilized, both during and after surgery, and practically all patients were kept in intensive care for at least 24 hr.

All the data were analyzed using a CDC 6000 computer and a suitable program developed in conjunction with the Department of Mathematics of the Tel Aviv University. All values of *p* less than 0.05 were considered statistically significant. The number of men in this series was slightly higher than the number of women, and emergency cases accounted for almost 40% of the group (Table 1).

Almost two-thirds of the patients had some involvement of the vital system, the cardiovascular system being by far the most frequently involved (45%) (Table 2). We have adopted, for this study, the ASA classification for estimating physical fitness as described by Owens et al (7). We have, however, modified and simplified it by combining Owens category 1 and 2 as well as category 4 and 5 into single categories, as there did not seem to be a clinical or statistical reason to preserve all five categories.

Four large diagnostic groups accounted for almost all patients: biliary; intestinal obstruction and acute abdomen; peptic ulcer; and intraabdominal malignancy. Operations on the biliary tract accounted for almost one-third of the patients in this group.

There was a slight predominance of female patients (1.4:1); however, this was much less than the ratio encountered in biliary surgery of younger patients (1:5). Choledocal exploration was performed in 43% of the patients. Stones were found in 90% of those explored.

Eliminating biliary surgery, the largest subgroup in this category was intestinal obstruction, accounting for almost one-quarter of the patients. Most intestinal obstructions in this age group were caused by incarcerated hernias and mechanical obstruction due to adhesions. Other, less frequent causes were vascular events and malignancy. Other emergency cases were for gastrointestinal bleeding, trauma, splenectomy, and various other explorations. One hundred and seven patients underwent surgery for peptic ulcer, the most common benign condition (except for biliary procedures) requiring abdominal sur-

TABLE 4

Major Diagnostic Groups, Malignant Conditions, 453 Cases

	Cases(%)
Location of tumor	
Stomach and esophagus	105(23)
Colon and rectum	254(56)
Pancreas	52(11)
Misc.	42(10)
Condition of tumor	
Curative resections	313(69)
Palliative procedures	68(15)
Laparotomy only	72(16)
Emergency cases	80(17)
Intestinal obstruction	38
Bleeding	25
Peritonitis and perforation	17

TABLE 5

Procedures Performed

	Cases(%)
Benign cases—547	
Simple cholecystectomy	162(30)
Cholecystectomy + choledocotomy	92(17)
Stomach and duodenum (vagotomy included)	98(18)
Appendectomy	34(6)
Lysis of adhesions	43(8)
Misc. procedures	118(21)
Malignant cases—453	
Resections	
colon & rectum	216(47)
stomach & esophagus	66(14)
Misc.	31(8)
Palliative procedures	68(15)
Laparotomy only, with or without biopsy	72(16)

TABLE 6

Postoperative Complications

Wound infection	96
Other septic	72
Respiratory	120
Thromboembolic	24
Cardiac	95
Burst abdomen	28

TABLE 7

Postoperative Hospital Stay

	No.(%)
1–10 days	374(37)
11–20 days	465(47)
21 days +	161(16)

TABLE 8
Mortality: General Data (136 Cases, 14%)

Sex	Ratio	%
Males	69:541	12.7
Females	67:459	14.6

After deduction of patients with inoperable tumors, ratio was 94:860, mortality 10.9%.

TABLE 9
Mortality by Age Group and ASA Class

	Cases(%)
Age	
70–74	48:573(8.4)
75–79	50:264(18.9)
80 and above	38:163(23.3)
chi square 31.099 $p < 0.001$	
ASA Class	
ASA 1	27:367(7.4)
ASA 2	55:468(11.8)
ASA 3	54:165(32.7)
chi square 63.156 $p < 0.001$	

TABLE 10
Mortality by Type of Surgery and Condition

	Cases(%)
Type of Surgery	
Emergency	77:391(19.7)
Elective	59:609(9.7)
chi square 22.613 $p < 0.001$	
Condition	
1:benign	50:547(9.1)
2:malignant operable	42:313(13.4)
3:malignant inoperable	44:140(31.4)
chi square 40.914 $p < 0.001$	

TABLE 11
Mortality by Major Diagnosis

	Cases(%)
Biliary surgery	5:254(2.1)
Peptic ulcer	10:107(9.7)
Benign intestinal obstruction	16:70 (22.9)
Appendicitis	1:34 (2.9)
Malignant tumors of colon and rectum	31:253(12.3)
Malignant tumors of stomach and esophagus	24:104(23.1)
Malignant tumors of pancreas	27:96 (28.1)
chi square 68.609 $p < 0.001$	

gery in the elderly (Table 3). Half the patients were operated on as emergencies, and preference for simple and definitive procedure was implemented by the frequent performance of truncal vagotomy.

Forty-five percent of all the patients had malignant disease (Table 4); more than half the malignant conditions were tumors of colon and rectum. Curative resections in this group were possible in only 69% of the cases, about one-third being inoperable at the time of surgery. Therefore, either a palliative procedure or a nontherapeutic laparotomy was undertaken. More than half the benign conditions were emergencies; only 17% of the procedures in malignant conditions were performed as emergency, mostly for intestinal obstruction (Table 4). Procedures performed are shown in Table 5, postoperative complications in Table 6, and postoperative hospital stay in Table 7.

Results

The general mortality in this series was 14% (Table 8); however, after exclusion of patients with terminal cancer, the mortality was 10.9%. After preliminary screening of all the factors studied, including sex, duration of surgery, use of antibiotics, type of incision, length of preoperative symptoms, many were found to be nonsignificant in predicting mortality. We focused our attention on five highly significant factors: age group (70–74, 75–80, 80 and above); three modified ASA classes of physical fitness; the timing of surgery as elective or emergency; condition, defined as either benign, malignant operable, or malignant inoperable; major diagnostic groups, without regard for the urgent or elective nature of the operation.

We deliberately excluded operative findings and nature of the procedure performed, because such data were not available for formulation of the prognostic index prior to surgery. Age was found to be a highly discriminating factor (Table 9), as was ASA category (Table 9).

The mortality in group ASA 1 was 7.4%; in ASA 3, 32.7%. Both age and ASA classification were statistically highly significant. Emergency versus elective procedure (Table 10) was another highly discriminating and statistically significant factor, as was the division into benign, malignant, and inoperable cases (Table 10); in this last category, mortality was 31.4%.

The major diagnostic groupings, as chosen in this study (Table 11), were equally discriminating. The lowest mortality was observed in biliary surgery (2.1%) and acute appendicitis (2.9%). The highest mortality was observed in tumors of the pancreas (28.1%). The most ominous predictive factors in this series were:

age 80 and above	23.3%
ASA category 3	32.7%
inoperable malignancy	31.4%
generalized peritonitis	23.5%
tumor of pancreas	28.1%

Moreover, in patients in whom two or more of those ominous factors were present, mortality was above 50%.

Discussion

Before 1950 major surgical procedures in the old and the very old were generally avoided. With the tremendous progress in postoperative care and anesthesia, more and more operations were attempted, some surgeons suggesting that age per se should not be a major consideration in formulating the indications for surgery.

The present study shows that the decline in operative mortality in the groups considered has been less dramatic than expected and highly selective. Technological advances such as cardiac surgery, hemodialysis, and intensive care have been limited in their usefulness to some extent by presenting the surgeon with further emergency situations in patients with deteriorating vital systems as well as many with terminal carcinomatosis (8–10).

Marked progress can be seen in this series with regard to all elective cases, both benign and malignant, which were operable. Such situations can be handled successfully in the great majority of cases provided they do not belong to ASA category 3 (11–14).

Emergency situations, so frequent in abdominal surgery of the very old, can be solved very successfully in acute biliary complications, appendicitis, bleeding duodenal ulcer, and mechanical small-bowel obstruction using early surgery (15–17). On the other hand, in emergencies where generalized peritonitis or carcinomatosis is present, a very high mortality in the elderly has to be anticipated. In patients who have two primary aggravating factors (for example, a patient with metastatic malignancy and peritonitis; patients over 80 with severe heart disease; patients with carcinoma of the pancreas and severe liver disease), prohibitive mortality can be expected, and the definite preference should be for nonsurgical methods. In the most extreme, "hopeless" cases, all active therapy should be avoided.

The policy in this series of cases, in regard to acute and subacute cases, has been early and definitive surgery. It is the opinion of the authors that this policy contributed to the lower mortality in situations such as cholecystitis, appendicitis, peptic ulcer, and small-bowel obstruction. This opinion is confirmed to some extent by the data published regarding those conditions (18, 19). Can one expect a further lowering of mortality in abdominal surgery of the aged? As a conclusion of the data in this study, one may attempt to lower the mortality further in this problematic group by diligently exercising clinical judgment in three areas:

1. Diagnosing early abdominal emergencies and acting swiftly and vigorously whenever possible
2. Early diagnosis of abdominal malignancies, particularly in the colon and rectum, and performing surgery more often in the operable stage
3. In cases in which consideration of prognostic factors indicates almost certain operative mortality, advising the family and the patient against surgery and using nonoperative therapy for palliation and cure

It is hoped that the precise knowledge of prognostic factors in geriatric surgery will help the surgeon make the necessary, difficult decision with wisdom and authority and contribute to the improvement of results achieved.

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Neurosurgical Approach to the Aging Patient

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Abstract

We have studied 79 elderly patients over the age of 65 years who have undergone neurosurgery. By neurosurgical pathology they divide into two main groups: intracranial lesions, 38 patients; spinal lesions, 41 patients. We found that 63% of the patients became independent, 18.5% partially dependent, 12% completely dependent (most of the patients in this group had severe head injury); 6.5% died (most of these patients had malignant diseases or severe craniocerebral injury). The results correlated with the state of progression of the disease and the nature of the lesion and the associated diseases. The postoperative results justify an active neurosurgical approach in elderly patients.

In the past, radical neurosurgical operations were not frequently performed in elderly patients (1–6). Nowadays, with the increasing longevity of the population, the number of geriatric patients requiring neurosurgical intervention has risen (1, 2, 5, 7). As a result of improved diagnostic methods, advances in neurosurgical techniques, and modern anesthesia, elderly patients can be more easily exposed to major neurosurgical procedures with good results (1–3, 7). This study is of a group of elderly patients over the age of 65 years with advancing neurosurgical disability who underwent elective or emergency radical neurosurgery. Outcome was satisfactory in the majority of patients.

Patients and Methods

This retrospective study focussed on 79 geriatric patients who underwent diverse neurosurgical procedures (Table 1). Mean age by sex was 70.95 years for men and 67.95 years for women (Table 1). Some typical cases are presented as an example of the diverse neurosurgical diseases. Postoperative results are reported.

Case 1. A 67-year-old woman developed organic mental syndrome, headaches, right hemiparesis, aphasia, and loss of vision in the left eye. Her general status worsened progressively over two years. Skull x-rays showed a marked thickening of the sphenoid ridge. Axial computerized tomography of the brain revealed a huge homogeneous mass in the left frontal region.

A left frontal craniotomy was carried out, and a meningotheliomatous meningioma, 8cm in diameter, arising from the internal third of the sphenoidal ridge and adjacent planum sphenoidal, was totally removed. Postoperatively, the hemiparesis and aphasia disappeared, she recovered vision in the left eye, and the organic mental syndrome improved. Axial computerized tomography of the brain showed complete tumor removal. After a rehabilitation period of 3 months, she returned to normal function and is fully independent in activities of daily living.

Case 2. A 75-year-old woman had progressive headaches, mental disturbances, and left hemiparesis over two months. One month before admission, she became hemiplegic and gradually stuporous. Computerized tomography of the brain revealed a huge mass occupying the right frontal region.

A right frontal craniotomy was performed; a

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TABLE 1
Operations Performed on 79 Elderly Patients

Operation	No. of operations	M:F	Mean age M:F
Craniotomy or craniectomy			
Benign intracranial lesion	16	7:9	69:68.1
Malignant intracranial lesion	11	6:5	68.2:71.25
Burr holes or craniectomy			
Acute traumatic or chronic subdural hematomas	7	5:2	77.75:67
Laminectomy			
Benign spinal lesion	26	12:14	70.3:68.6
Malignant spinal lesion	15	13:2	70.4:67
Ventriculoperitoneal shunt	4	2:2	71:65.5
Total	79	45:34	70.95:67.95

M:F, males:females.

huge glioblastoma multiforme that occupied most of the frontal lobe was found and removed by right frontal lobectomy. The patient was rehabilitated and was in good condition. She could function as a housewife until recurrence of the tumor, from which she eventually succumbed 7 months later.

Case 3. A 75-year-old man experienced, one month before admission, low back and right sciatic pain and muscle weakness and sensory disturbance in the right leg. In the last two weeks before admission, he was not able to walk. On admission, he showed marked weakness of dorsiflexion of the left foot (partial drop foot) and hypoesthesia of the left leg. X-rays of the spine showed osteoporotic and spondylolytic changes at $L_{2,3,4}$. A myelogram showed spinal stenosis and total block at $L_{3,4}$ level.

A decompressive laminectomy $L_{2,3,4}$ was carried out; prolapsed disc L_3-L_4 was removed. Postoperatively, muscle weakness and sensation of right leg returned to normal. After a rehabilitation period, in which intensive physiotherapeutic treatment was given, the patient was able to walk freely and he returned to complete activity. Two years later, he was in good condition.

Case 4. A 69-year-old man was admitted for radicular thoracic pain for 6 months and bilateral weakness of lower extremities that appeared a week prior to admission. On examination, he had marked spastic paraparesis, bilateral pyramidal signs, and hypoesthesia with sensory level at D_6. Spine x-ray showed a "white vertebra" body at D_6. Myelography showed a partial stop at D_8 and a complete stop at $D_{6,7}$.

Laminectomy D_5 to D_9 was performed. An extensive epidural mass of metastatic prostatic carcinoma, compressing the spinal cord posteriorly and to the right, was removed. After a rehabilitation period, in which physiotherapeutic and oncologic treatment were given, the neurologic disturbances disappeared. Three years later, he was in the same good condition and fully active.

Results

Among the 79 patients we studied, 27 were found to have brain tumors, either benign (meningioma, neurinoma) or malignant (glioma, sarcoma, brain metastasis). Head trauma, present in 7 patients, was associated with acute posttraumatic hematomas in 4 and chronic subdural hematomas in 3. In 4 patients normal-pressure hydrocephalus was found and ventriculoperitoneal shunt was performed. Of the 79, 41 had spinal lesions; 21 had spinal stenosis, with cord compression; 5 had meningioma; 13 had spinal metastasis of variable origin; and 2 suffered from spinal malignant primary tumors.

Postoperative follow-up after one year showed (Table 2) good improvement (patient fully independent) in 51.85% of the patients who underwent operation for brain tumor, mild improvement (partially dependent) in 22.22%, poor results (completely dependent) in 18.5%; 7.4% died. Among the patients with chronic subdural hematoma, 79.9% showed good improvement. Surgical mortality was high in patients with acute posttraumatic hematoma. Of the patients with spinal lesion, 70.75% showed good improvement (fully independent), 19.50% showed mild improvement (partially dependent), and 7.31% showed poor results (completely dependent); 2.45% died.

Discussion

Surgeons nowadays tend to advise operation in elderly patients more than they did some decades ago (4–6, 8). Surgery for the elderly patients has recently developed and advanced (1–5, 7, 9), particularly because longevity has increased (1–5, 10). It is now believed that elective operation is no less important for elderly patients than for younger ones (4, 5). Older patients tolerate the most extensive elective operations when they are still in good preoperative general condition, but they poorly tolerate emergency surgical procedures when illness or some other related disease brings them to a poor general condition (1, 4, 5, 9). The elderly patient tolerates complications very poorly, so these complications should be intensively treated, to avoid an adverse influence on postoperative survival (1, 4, 5, 9).

Better methods of diagnosis have been developed. In the past, diagnosis was made by invasive

TABLE 2
Postoperative Results after One-Year Follow-up, 79 Elderly Patients

Operation	Functional level: Independent	Partially dependent	Completely dependent	Died
Craniotomy or craniectomy				
Benign intracranial lesion	13	3	—	—
Malignant intracranial lesion	1	3	5	2
Burr holes for acute traumatic or chronic subdural hematomas	4	1	—	2
Laminectomy				
Benign spinal lesion	22	3	—	—
Malignant spinal lesion	7	5	3	1
Ventriculoperitoneal shunt	3	—	1	—
Total	50	15	9	5

procedures such as arteriography and pneumoencephalography. There were always hesitations to perform the kind of procedure that endangered the patient's life or threatened morbidity, resulting in irreversible diagnostic delay (3–5).

Also curative period was missed for operable neurosurgical diseases because they were interpreted as results of aging arterioscleroses. The introduction of the radioactive brain scan and the computerized axial tomography that has nowadays become an almost routine procedure, results in an early and accurate diagnosis of the neurosurgical diseases.

The improvement of the neurosurgical techniques, especially the development of microneurosurgery, allows us to perform radical operations with minimal bleeding and brain damage, with less risk to the patient's life and much better functional results (1–3).

The improvement of anesthesia techniques and intensive care methods were positive factors (4, 5, 10, 11). The most frequent brain tumors in the elderly according to the literature are glioblastoma and meningioma (1, 2, 7). Also occuring frequently are hydrocephalus and subdural hematoma (6, 8). In our cases the conclusion is that neurosurgical operations in the elderly patient is worthwhile, and can be tolerated well especially with an early diagnosis, when the elderly patient is still in a good general condition. Mortality is high in patients with severe head trauma and acute intracranial hematoma, as was the case in our experience. Good results were obtained in patients operated on for chronic subdural hematoma.

We obtained good results in the radical operations even in cases of malignant diseases, improving considerably the quality of life of the elderly patient. We recommend a rapid, active and radical operative approach for neurosurgical diseases as the treatment of choice in the elderly patient.

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Assessment of Serum Angiotensin-Converting Enzyme As a Marker of Activity in Sarcoidosis: A Study of 31 Patients With Erythema Nodosum

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Abstract

Serum angiotensin-converting enzyme levels were determined in 31 patients with clinically active sarcoidosis manifested by erythema nodosum. Only 54.8% of the patients had elevated enzyme levels. Serum angiotensin-converting enzyme is not a reliable indicator of activity in patients who have acute sarcoidosis with erythema nodosum. The Kveim test was positive in all 31 patients, suggesting that a positive Kveim-Siltzbach test is a reliable marker of acute sarcoidosis with erythema nodosum.

Most authorities agree that erythema nodosum occurs in acute sarcoidosis and is a reliable clinical indicator of active disease (1, 2). Many observers have strongly suggested that elevated serum angiotensin-converting enzyme is an in vitro marker of activity in sarcoidosis (3–7). In order to assess the value of this enzyme as such a marker, serum angiotensin-converting enzyme was determined in 31 patients with clinically active sarcoidosis as evidenced by the presence of erythema nodosum.

Materials and Methods

Thirty-one patients of the Sarcoidosis Clinic at The Mount Sinai Medical Center, New York, with erythema nodosum, from 1976 through 1982, had serum angiotensin-converting enzyme determinations performed. The diagnosis of sarcoidosis was established by a positive Kveim-Siltzbach test in all 31 patients. Kveim-Siltzbach antigen was produced and the intracutaneous test performed according to the method of Chase and Siltzbach (8). There were 6 males and 25 females with a mean age of 40.1 years. Thirteen patients were Hispanic, 9 black, and 9 white. Chest radiographs were staged by two independent observers.

Enzyme levels were determined in the first 8 patients by radioimmunoassay using a radiolabeled acylated tripeptide as a substrate, measuring activity by release of ^{3}H (Ventrex). Normal values by this method were 84.5 nanomoles/m/ml ± 20.5; an enzyme level greater than 125 was considered elevated (9). The spectrophotometric method of Cushman and Cheung (10) as modified by Lieberman (11) was employed in the determination of enzyme levels in the subsequent 23 patients. Normal values by this method were 27.8 ± 6.0; a value greater than 35 was considered elevated. No patient received adrenocorticosteroid therapy during the study.

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Results

Serum angiotensin-converting enzyme level was elevated in 54.8% of the 31 patients with sarcoidosis manifested by erythema nodosum (Table). Twenty-seven patients had radiographic stage I disease. Sixteen of these had elevated serum angiotensin-converting enzyme. One patient had stage 0 radiograph, and 3 had stage II. Of these latter 4 patients, only 1 had elevated serum angiotensin-converting enzyme. Thus, 16 of the 17 patients with elevated serum angiotensin-converting enzyme had radiographic stage I sarcoidosis. All 31 patients had a positive Kveim-Siltzbach test.

TABLE

SACE and Kveim-Siltzbach Test in 31 Patients with Sarcoidosis and Erythema Nodosum, by X-Ray Stage*

	Stage					
	0	I	II	III	Total	%
Elevated SACE	0	16	1	0	17	54.8%
Normal SACE	1	11	2	0	14	45.2%
Positive K-S†	1	27	3	0	31	100.0%

* SACE, serum angiotensin-converting enzyme.

† K-S, Kveim-Siltzbach.

Discussion

Sarcoidosis is a disease that most often runs its course within 6 months to 2 years, with or without therapy, leaving little or no clinical evidence of disease. However, in a significant number of patients sarcoidosis progresses, or persists, manifesting ocular, cutaneous, osseous, joint, neuromuscular, myocardial, or pulmonary abnormalities. In some of these patients the acute sarcoid lesions have been replaced by fibrosis and hyalinized granulomas, which cannot be expected to respond to steroid therapy. In others, active granulomas, which may be responsive to medication, persist.

The search for indicators of activity that may serve as a guide to therapy has led to a number of varied proposals. At the Ninth International Congress of Sarcoidosis in Paris, September 1982, a proposed list of markers of activity in sarcoidosis included a positive Kveim-Siltzbach test, demonstration of epithelioid granulomas by organ biopsy, hypercalcemia, positive gallium citrate scan, elevated serum angiotensin-converting enzyme, and relative lymphocytosis in bronchoalveolar lavage fluid. Most of these tests have one or more of the following drawbacks: unavailability, expense, patient discomfort and morbidity, and low sensitivity.

A simple, noninvasive, inexpensive, readily available in vitro test, such as the serum angiotensin-converting enzyme, would be of great value in assessing activity in sarcoidosis, if it proved to be positive in the great majority of active patients. However, our data revealed that only 54.8% of patients with erythema nodosum and sarcoidosis, a universally accepted clinical stage of active sarcoidosis, had elevated serum angiotensin-converting enzyme levels. This is not surprising, since Silverstein et al (12) have demonstrated that the enzyme is produced by the sarcoid granulomas and that enzyme level may reflect the total body mass of sarcoid tissue. Several studies have shown that the enzyme is elevated with the greatest frequency in patients with radiographic stage II and III sarcoidosis, particularly when there is clinical evidence of extrathoracic involvement. The majority of our patients with erythema nodosum had radiographic stage I patterns, and none had evident extrathoracic disease. Of the 31 patients, 28 had stage 0 or stage I, and only 3 had stage II radiographs. None had stage III radiographs.

Many investigators have reported excellent correlation of serum angiotensin-converting enzyme with activity of sarcoidosis and have stressed its value in following the course of the disease, particularly when patients are receiving steroid therapy (13). Schoenberger et al (14), on the other hand, have noted a lack of correlation of enzyme value and the relative lymphocytosis seen in the bronchial alveolar lavage fluid or uptake of ^{67}gallium in the lungs of their patients with active sarcoidosis. Overall, elevated enzyme levels have been reported in 50%–80% of patients with sarcoidosis (15, 16). Thus, a significant number of patients with sarcoidosis have normal levels of this enzyme. Sarcoidosis patients with erythema nodosum appear to be such a group. Grönhagen-Riska et al (17) have noted that in patients with sarcoidosis and normal levels of the enzyme, the enzyme level decreases further when steroid treatment is administered. Recognizing that a significant number of patients with sarcoidosis have normal enzyme levels, they propose that even when the enzyme value is normal, subsequent decreases in value are a measure of suppression of the disease. Since none of the 31 patients in this study received steroid therapy, we were unable to confirm this finding.

Romer (18), in a report of serum angiotensin-converting enzyme levels in 56 patients with "newly detected sarcoidosis," notes that 70% had elevated enzyme levels. In a subgroup of patients with erythema nodosum, only 1 of 7 had elevated enzyme levels; subsequent levels were elevated in all patients in this subgroup with erythema nodosum. In 11 patients in our group of 31 with erythema nodosum, follow-up tests of enzyme levels were performed and all remained normal. This discrepancy may be due to the uniform clearing of the disease in all 11 who had serial tests of enzyme level in our study.

The Kveim-Siltzbach test is positive in approximately 80% of patients with sarcoidosis (19). All 31 patients in this study tested positive. Siltzbach (20) has shown that many patients who have positive results early in the disease may test negative later as the disease abates or stabilizes. Our study, in which all 31 patients with erythema nodosum had positive results, and a previous study, in which 91 of 94 patients with erythema nodosum were also positive on this test (21), suggest that a positive Kveim-Siltzbach test is a sensitive marker of activity in acute sarcoidosis with erythema nodosum. When serum angiotensin-converting enzyme is elevated in sarcoidosis, it is a reliable indicator of disease activity. However, in the 20%–40% of patients with normal serum angiotensin-converting enzyme, particularly when erythema nodosum is present, serum angiotensin-converting enzyme does not accurately detect active sarcoidosis.

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Pulmonary Artery Catheter-Associated Thrombocytopenia: Effect of Heparin Coating

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Abstract

The authors studied the effects of heparin coating of pulmonary artery catheters on platelet counts in patients undergoing aortocoronary artery bypass grafting. Sixteen patients were assigned randomly to two groups of eight patients to receive either heparin-coated (group I) or nonheparin-coated (group II) pulmonary-artery catheters prior to the grafting surgery. Platelet counts were measured prior to catheter insertion, 6 hr after insertion, and 24 hr after insertion. Platelet counts decreased in both groups; no statistically significant difference emerged between groups. These results suggest that heparin coating offers no advantage in reduction of platelet consumption associated with pulmonary arterial catheters.

Flow-directed pulmonary arterial catheters are associated with thrombocytopenia in animals (1) and humans (2, 3). Similar decreases in platelet count have been reported in patients undergoing aortocoronary bypass grafting (2) and in nonsurgical, intensive-care-unit patients during a period of 24 hr following insertion of such catheters (3). Increased platelet counts were noted after removal of these catheters in both study populations. A recent study demonstrated decreased, short-term, catheter-induced thrombogenicity in humans when catheters coated with heparin were used (4). No studies to date have demonstrated that thrombocytopenia is prevented by heparin bonding. This study compares the effects of heparin-coated and noncoated pulmonary artery catheters on platelet counts during the 24 hr following aortocoronary bypass.

Methods and Materials

Sixteen patients undergoing aortocoronary bypass grafting were studied. Approval for this study was obtained from the University of Pennsylvania committee on studies involving humans, and informed consent was obtained from all patients. Subjects were assigned randomly to one of two groups of eight patients, to receive either heparin-coated (group I) or non-heparin-coated (group II) pulmonary artery catheters. Gould heparin-coated 7F catheters (#SP5107), supplied to us by the manufacturer, were used for group I patients and Gould 7F non-heparin-coated catheters (#SP5107, lot #51040) were used for group II patients. The catheters were inserted via internal or external jugular veins and remained in situ for 24 hr. All platelet counts were performed in triplicate by phase-contrast microscopy on citrated samples obtained from radial artery catheters. Samples were obtained prior to catheter insertion, 6 hr after catheter insertion (postcardiopulmonary bypass), and 24 hr after catheter insertion. Hematocrits were recorded at the times

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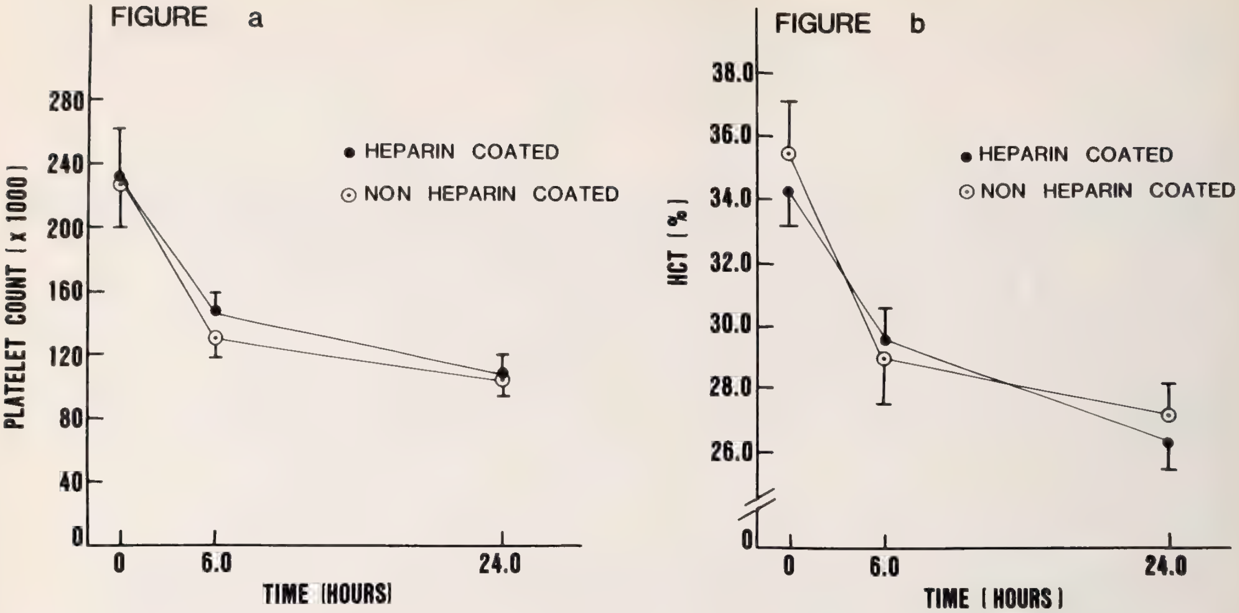

Fig. (a) Platelet count mm^3 (× 1,000) in heparin-coated catheter group (solid circles) and non-heparin-coated catheter group (open circles) at control, 6-hr, and 24-hr sample times. (b) Hematocrit (%) of heparin-coated catheter group (solid circles) and non-heparin-coated catheter group (open circles) at control, 6-hr, and 24-hr sample times.

of platelet sampling. Statistical analysis was performed using within-subjects, two-factor analysis of variance (ANOVA) or Student's test for unpaired data where applicable.

Results

Premedication, anesthetics, and postoperative medications were similar in both groups. No patients being treated with preoperative aspirin, intravenous heparin, intravenous nitroglycerin, or other antiplatelet medications were included in this study, although all patients received cephalosporins. There was no difference between the heparin-coated and non-heparin-coated groups in either age, bypass time, postoperative blood loss, or postoperative blood replacement (Fig.). No patient received platelet transfusion in the perioperative period. There was no statistically significant difference between the two groups in either platelet count or hematocrit at any sampling time (Fig.). In both groups, there was a significant decrease at the 95% confidence level in platelet counts from the control sample to the 6-hr postinsertion sample. The decrease in platelet count from the 6-hr sample to the 24-hr sample was significant at the same confidence level in the heparin-coated group and not significant in the non-heparin-coated group.

Discussion

Thrombosis is a known complication of short- and long-term pulmonary artery catheterization (5). Non-heparin-coated pulmonary artery catheters have been reported to have up to a 100% incidence of surface thrombi (5). In a recent study by Chastre et al (6), a 66% incidence of internal jugular vein thrombosis was diagnosed by venography performed 12 hr after removal of pulmonary arterial (PA) catheters. Documented complications of these catheter-induced thrombi are relatively few and include a case reported by Swan et al (7) of a fatal superior vena caval thrombus surrounding the shaft of a PA catheter. Foote (8) reported 9 of 125 patients (7%) studied had catheter-induced pulmonary vascular lesions; in only 2 of these patients could emboli from catheter thrombosis be implicated as a probable cause. In addition to ischemic pulmonary lesions, catheter thrombi can also cause damping of pulmonary artery pressure tracings and inaccuracy of thermodilution cardiac output determinations (9).

PA-catheter-induced thrombogenicity is believed to result from an interaction of the patient's blood with certain textural and chemical properties of the catheter surface (4). Therefore, the polymerization of heparin to quaternary ammonium compounds and coating of PA catheters with these complexes has been proposed to decrease the incidence of catheter thrombogenicity (10). Thrombogenicity, as diagnosed by visual inspection of PA catheters, was decreased by heparin coating in at least one study (4).

Several studies in animals and humans demonstrate thrombocytopenia when PA catheters are used (1–3). Kim et al (2) reported an increased consumption of platelets with PA catheter versus central venous catheter insertion in patients undergoing aortocoronary artery bypass grafting. This thrombocytopenia was reversed by catheter removal. The increased thrombocytopenia in the PA catheter group may have been a function of the greater surface area of the PA catheter. No studies to date have assessed the prevention of thrombocytopenia by the use of heparin coating of PA catheters.

The present study has shown no statistically significant difference in platelet counts 24 hr after insertion of either heparin- or nonheparin-coated PA catheters. Although the incidence of visual thrombi on the surface of catheters is less with heparin-coated catheters, the similar decrease in platelet counts with both heparin and non-heparin coating may be indicative of local activation of clotting mechanisms and resultant platelet consumption in the vicinity of the catheter. Other possible explanations for the similarity in platelet decrease are the effects of cardiopulmonary bypass on platelet function, hemodilution, and the washoff of heparin from the catheter surface while in situ (10). Hemodilution cannot be ruled out as a contributing factor to the similarity in platelet decrease in both groups, because a similar decrease in hematocrit has been demonstrated (Fig. B). It is not known how long heparin remains on the surface of a coated catheter while in situ, although one study has shown markedly decreased platelet accumulation on heparin-coated catheter surfaces for up to 48 hr in situ (11).

In conclusion, present methods for heparin coating of PA catheters offer no advantage in prevention of catheter-induced thrombocytopenia in patients undergoing aortocoronary bypass grafting.

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Ultrastructural Analyses of Developing Sternocostal Cartilage in the (ch) Hydrocephalic Mouse

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Abstract

Using technics of stereology we estimated the collagen, proteoglycans and extracellular space in electron micrographs of sternocostal cartilage of fetal and newborn ch+ hydrocephalic and control mice. The newborn hydrocephalic mice showed a slight increase in the volume density of proteoglycan granules, a slight decrease in the volume density of collagen fibrils and no change in the volume density of extracellular space compared to fetal animals. In contrast, the newborn controls showed an increase in the volume density of collagen fibrils and proteoglycan granules and a decrease in the volume density of extracellular space. The newborn hydrocephalic mice showed a lower volume density of collagen and proteoglycan granules and a higher volume density of extracellular space than controls. These stereologic estimates correlated with the lower protein and higher water contents of hydrocephalic mice and with our own subjective estimates of the size of collagen fibrils and proteoglycan granules. Our findings further corroborate our proposal that the sternocostal cartilage of the hydrocephalic mouse fails to develop because of a biosynthetic defect of proteoglycans.

In our previous studies on ch+ hydrocephalic mice with a congenital, recessively inherited, lethal hydrocephalus and multiple defects of central and autonomic nervous system, skin, and urogenital system, we demonstrated abnormalities of cartilage and endochondral bone formation (1, 2). In this report, we present the results of our quantitative ultrastructural measurements and estimates of protein and water contents of sternocostal cartilage of fetal and newborn ch+ hydrocephalic and normal satin control mice.

Materials and Methods

Fetal and newborn hydrocephalic and satin control mice were divided into groups of 4 to 12 animals. Sternocostal cartilage was excised and portions submitted for electron microscopic study using methods described previously (1, 2).

The volume and surface densities of collagen and proteoglycans and the volume density of extracellular space were determined from electron micrographs at a magnification of 40,000× using point and line intersection counting technics of stereology (3). A grid of 2 cm squares drawn on an acetate sheet was laid on the electron micrographs and the points (upper right hand corners of the squares) hitting collagen, proteoglycans, and extracellular space were counted. We then counted the intersections of the collagen bundles and of the proteoglycans with the horizontal lines of the grid. The volume and surface densities were then computed using standard stereologic equations (3). The diameters of the proteoglycan granules and the collagen fibrils in the extracellular space of different electron micrographs from

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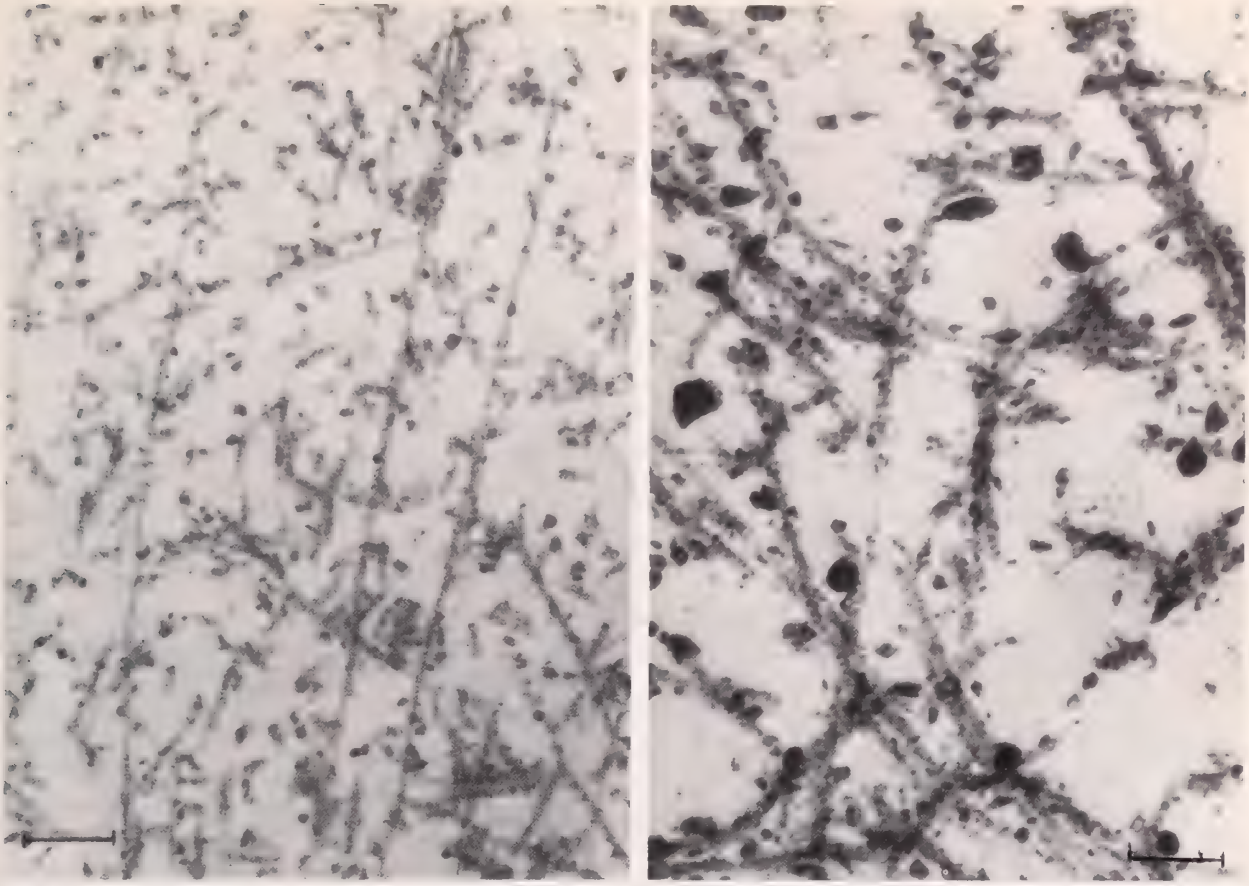

Fig. 1. Left Electron micrograph of elongated, branching collagen fibers with attached electron-dense granules (proteoglycans) and interfibrillar granules in stellate reticulum in a fetal satin mouse. Bar = 0.1 μm. **Right** Electron micrograph from developing central sternal region of fetal ch mouse containing collagen fibrils in clumps with fewer, but larger, electron-dense granules (proteoglycans). Bar = 0.1 μm.

the four groups of mice were measured by our previously described method (2).

Then we estimated the protein and water content of the remaining unfixed sternocostal cartilages. Three to six sternocostal cartilages from each group were pooled, weighed, and dried in a vacuum oven at 60°C for 24 hours and reweighed. The pooled samples were defatted with two 24-hr extractions in cold ether-alcohol and weighed again. Percent of water and of protein were then calculated from the wet, dry and defatted dry weights.

Results

Our subjective estimates of collagen, proteoglycans, and extracellular space were similar to our previous findings (2). Compared to controls, the hydrocephalic mice had fewer but larger aggregates of collagen fibrils, fewer and bigger proteoglycan granules in the fetal animals (Fig. 1) and larger extracellular space, particularly in the newborn animals. When we compared the fetal with the newborn animals, we noted a slight decrease in the size, but no change in the number, of collagen fibrils and proteoglycan granules, and a moderate decrease of extracellular space in the newborn hydrocephalic mice. In the controls, the size of collagen fibrils and proteoglycan granules did not change, but the extracellular space showed a marked decrease in the newborns.

In the fetal animals, the hydrocephalic mice showed larger diameters of collagen fibrils and proteoglycan granules than controls (Table 1). In the newborn animals, however, only the diameter of collagen fibrils was bigger in the hydrocephalic mice. Comparison of fetal and newborn animals showed a decrease in the diameters of collagen fibrils and proteoglycan granules in only the newborn hydrocephalic mice.

Hydrocephalic fetal and newborn mice had lower protein and higher water content than controls (Table 2). The protein and water content did not change from the fetal to the newborn period in the hydrocephalic and control mice.

When we compared the hydrocephalic and control mice, we found no difference in the volume density of collagen, proteoglycan granules, and extracellular space in the fetal an-

TABLE 1

Diameter (nm) of Intercellular Proteoglycan Granules and Collagen Fibrils in the ch Murine Model

Genotype and age (no.)	Proteoglycan granule diameter (nm)	Collagen fibril diameter (nm)
ch+/ch+ fetal (13)		
mean	19.7 + 1.3	46.2 ± 4.9
variable range	11.5–27.1	20.8–87.1
median	20.6	41.6
ch+/ch+ newborn (4)		
mean	12.7 ± 3.5	30.9 ± 1.7
variable range	9.3–15.8	29.2–39.9
median	13.0	32.6
+sa/+sa fetal (8)		
mean	14.7 ± 1.2	13.1 ± 0.9
variable range	10.5–18.0	10.5–15.3
median	14.8	12.3
+sa/+sa newborn (4)		
mean	14.5 ± 0.3	15.1 ± 1.6
variable range	13.9–14.8	13.0–18.9
median	14.7	14.0

imals (Table 3). The surface density of collagen and the surface-to-volume ratio of collagen and proteoglycan granules were higher in the fetal hydrocephalic mice, but the difference was not significant. In the newborn animals, the volume density of collagen and proteoglycan granules were lower in hydrocephalic mice, but the difference was not significant. The volume density of extracellular space was, however, significantly higher in newborn hydrocephalic mice. The surface density of proteoglycan granules was also lower in the newborn hydrocephalic mice, but again the difference was not significant. The surface-to-volume ratio of collagen was higher, and proteoglycans lower, in the hydrocephalic newborn mice. Comparison of the newborn with the fetal animals showed no change in the volume density of collagen, proteoglycans, and extracellular space in the hydrocephalic mice. The surface density of collagen and proteoglycans also did not change in the hydrocephalic newborn, but their surface-to-volume ratios appeared to decrease. In the controls, the volume density of collagen and proteoglycans increased in the newborn animals, but the difference was not significant. The volume density of extracellular space was, however, significantly higher in the newborn controls. The surface density of proteoglycans increased in the newborn controls, but the difference was not significant.

TABLE 2

Summary of Substance Percentages in Developing Sternocostal Cartilages

	Fetal		Newborn	
	ch+/ch+	+sa/+sa	ch+/ch+	+sa/+sa
Protein	14.2	26.4	16.4	24.3
Water	85.0	71.8	83.1	73.8

Percentages are rounded to tenths and are a composite of pool averages.

Discussion

Our subjective ultrastructural observations of fewer proteoglycan granules in hydrocephalic mice compared to controls correlated with our biochemical finding of reduced acidic glycosaminoglycans (1). Because the acidic glycosaminoglycans of the proteoglycan macromolecules carry a high charge density, they have many polyanionic binding sites and can influence the diameter and the aggregation of collagen fibrils (4). That the hydrocephalic mice had larger proteoglycan granules did not argue against them having fewer glycosaminoglycans, because they also had fewer granules. This suggestion was supported further by our stereologic finding of lower volume and surface density of proteoglycan granules in the newborn hydrocephalic mice. The fetal hydrocephalic mice may not have shown a similar stereologic change because of sampling, that is, the quality of the electron micrographs precluded us from using as many animals for our stereologic counts. Nevertheless, all these estimates support our finding that hydrocephalic mice have reduced levels of glycosaminoglycans and fewer polyanionic binding sites (2). The lower volume densities of proteoglycan and collagen and the higher volume density of extracellular space in the newborn hydrocephalic mice correlated with their lower protein and higher water contents.

When we compared the fetal and newborn animals, our subjective ultrastructural estimates did not always show distinct changes in the hydrocephalic mice because of the variation among the animals and the irregular distribution of the collagen fibrils and proteoglycan granules in their cartilages. We detected a decrease in the size and a possible increase in the number of proteoglycan granules in the newborn, which suggested an increase in the number of acidic glycosaminoglycans. The lack of change in the volume or surface density of proteoglycan granules in the newborns, however, suggests that such an increase, if any, is small. Furthermore, our subjective impression that the newborns had more and smaller collagen bundles suggested growth of collagen fibrils, possibly the result of small increases of their proteoglycans. This

TABLE 3

Quantitative Ultrastructural Estimates

	Fetal		Newborns	
	ch+/ch+ n = 8	+sa/+sa n = 7	ch+/ch+ n = 4	+sa/+sa n = 6
Collagen				
Volume density mm^3/100 mm^3 tissue				
mean	35 ± 4	30 ± 6	28 ± 6	48 ± 7
range of values	19–47	7–51	12–34	14–58
median	39	40	33	55
Surface density mm^2/100 mm^3 tissue				
mean	130 ± 12	84 ± 22	90 ± 21	100 ± 15
range of values	91–197	24–180	26–112	29–124
median	138	92	109	114
Surface/volume ratio	3.7	2.8	3.2	2.1
Proteoglycans				
Volume density				
mean	20 ± 4	19 ± 5	28 ± 4	40 ± 9
range of values	4–42	6–41	15–35	24–81
median	20	18	32	34
Surface density				
mean	64 ± 10	53 ± 12	67 ± 10	121 ± 32
range of values	29–112	13–99	38–83	62–276
median	55	53	75	96
Surface/volume ratio	3.2	2.7	2.3	3.0
Extracellular space				
Volume density				
mean (water)	45 ± 6	50 ± 10*	45 ± 5**	13 ± 2**
range of values	20–76	16–82	31–74	5–19
median	48	55	39	13

* $p < 0.005$

** $p < 0.01$

growth of collagen fibrils, however, was not reflected in their volume and surface densities, which showed a statistically insignificant decrease. Because the volume density of proteoglycans increased as the volume density of collagen decreased, the volume density of extracellular space did not change in newborn animals. This finding correlated with the lack of change of protein and water content in newborn hydrocephalic mice. In the controls, we found an increase in the number, but not the size, of the more tightly packed collagen fibrils and proteoglycan granules in the newborns. These were reflected in the higher volume densities of collagen fibrils and proteoglycan granules and the lower volume density of extracellular space, but not in the protein or water contents. The collagen fibrils, the proteoglycan granules, the protein content, and the extracellular space or water content are, however, not strictly comparable because fixation, dehydration, embedding in plastic, and staining changes tissues prepared for electron microscopic examination.

We conclude that our stereologic estimates corroborate our previous findings of reduced levels of acidic glycosaminoglycans and fewer polyanionic binding sites in newborn hydrocephalic mice and our proposal that their sternocostal cartilage fails to develop because of a biosynthetic defect of proteoglycans (1).

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Bilateral Chylothorax Secondary to Subclavian Vein Catheterization: A Case Report

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Abstract

A case of bilateral chylothorax following percutaneous placement of a subclavian catheter is described. The pathophysiology associated with chylothoraces as well as the treatment of such complications is discussed. Physicians who are involved with the placement of central venous catheters should be aware of this newly reported complication.

Traumatic chylothorax, although uncommon, has been reported following a variety of surgical procedures (1–5). Similarly, complications resulting from placement of percutaneous subclavian catheters have been described. Herein we present a case of a bilateral chylothorax which developed shortly after placement of a right subclavian venous catheter. To our knowledge this is the first reported case in an adult of such a complication.

Case Report

A 20-year-old white man was transferred from another hospital with a left subphrenic abscess and bilateral pleural effusions. Three weeks prior to transfer he underwent a splenectomy for hereditary elliptocytosis. The immediate postoperative period was complicated by splenic bed hemorrhage which required reexploration for hemostasis. Subsequently he developed a left subphrenic abscess. One week prior to transfer, percutaneous drainage of the abscess was unsuccessfully attempted. It was then decided to begin total parenteral nutrition, for which a right subclavian central venous catheter was inserted infraclavicularly three days prior to transfer. The patient described difficulty with the catheter insertion, pain at the insertion site, and fluid drainage from under the right clavicle.

On arrival at our institution the patient was in moderate distress, complaining of substernal pain. His temperature was 39°C, pulse 128, respirations 24, and blood pressure 118/72. The physical examination was significant for "white material" oozing from the right subclavian puncture site, dullness to percussion and egophony on ausculation at the bases of both lung fields, and mild left-upper-abdominal tenderness. Initial laboratory data included white blood cell count, 21,200 mm^3, 74 segmented neutrophils and 10 lymphocytes; hemoglobin, 10.4 g/dl; and a chemistry panel within normal limits. Chest x ray showed bilateral pleural effusions and widened mediastinum. The subclavian catheter present on transfer was subsequently removed.

Evaluation of the pleural effusions consisted of an initial right thoracentesis, which yielded 1,400 ml of "milky" fluid whose red blood cell count was 3,200/mm^3 and white blood cell count, 5,000/mm^3. Cultures from this fluid, and all subsequent samples, were negative. Because the patient had previously received intravenous hyperalimentation including lipid emulsion, it was ini-

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tially thought that this effusion represented extravasation of Intralipid. A thoracostomy tube was inserted after an incidental pneumothorax complicated the diagnostic thoracentesis. One thousand milliliters of the same milky fluid was removed. Chest x ray demonstrated the widened mediastinum and bilateral effusions as well as a right pneumothorax (Fig. 1.) The patient underwent an exploratory laporatomy with drainage of the subphrenic abscess. Recovery from this procedure was relatively uneventful.

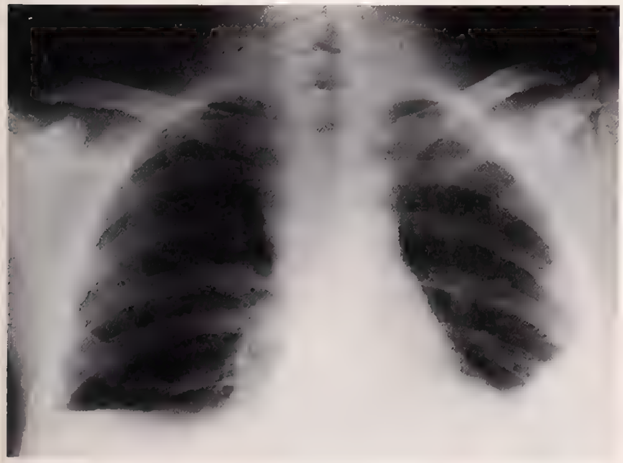
The chest tube, however, continued to drain approximately 50 ml/hr for the first 24 hr following surgery. Chest x ray revealed that the mediastinum was still enlarged and the left pleural effusion had increased. A left-sided chest tube was inserted with drainage of fluid identical in appearance to the right-sided drainage. Analysis of the pleural fluid revealed triglycerides, 882 mg/dl; cholesterol, 40 mg/dl; glucose, 54 mg/dl; protein, 3.4 g/dl; and phospholipid, 53 mg/dl. Based on the continued drainage of the fluid and the chemical analyses, the diagnosis of a bilateral chylothorax was made.

The chylothorax was treated conservatively with parenteral nutrition through a right internal jugular catheter, hydration, bed rest, and supportive care. Chylous drainage continued at the rate of 10–30 ml/hr for 48 hr, before stopping by the fourth postoperative day. Shortly thereafter the chest tubes were removed. During the time of chylous drainage the patient's serum protein had fallen from 6.5 to 4.8 g/dl and the serum calcium from 8.8 to 7.6 mg/dl. On postoperative day 10, the patient was discharged home in stable condition tolerating a normal diet. Discharge examination and chest x ray (Fig. 2) revealed no evidence of effusion and demonstrated normalization of the mediastinal appearance.

Discussion

Although uncommon, chylothorax is a potentially life-threatening complication. Over 50% of chylothoraces are secondary to disruption of thoracic duct flow by tumor, most commonly lymphoma (1, 2, 4, 6). Other etiologies are penetrating and blunt trauma and surgical procedures. The latter are usually associated with cardiovascular, esophageal, or head and neck surgery (1, 2, 4, 5). The reported incidence of postoperative chylothorax in these procedures is less than 0.5% (2, 7).

The anatomic position of the thoracic duct in the chest makes the development of a bilateral chylothorax extremely rare. Arising from the cisterna chyli, the thoracic duct passes through the hiatus of the right diaphragm into the thoracic cavity and then extends extrapleurally into the posterior mediastinum along the right anterior surface of the vertebral column. In the thorax the duct is in close proximity to the esophagus, descending aorta, and pericardium. It then crosses to the left side of the vertebral column between the fourth to sixth thoracic vertebrae and enters the superior mediastinum between the aortic arch and subclavian vessels. In the neck the duct arches 3–5 cm above the clavicle, passing anteriorly to the subclavian artery, vertebral artery, and thyrocervical trunk. It usually terminates into left jugular or subclavian veins, but wide anatomic variations have been reported. In the rare



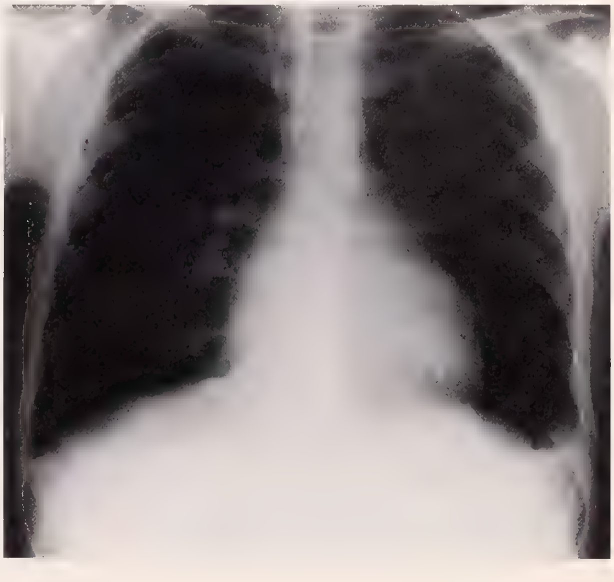


Fig. 1. Left Chest x ray demonstrating widening of the mediastinum.

Fig. 2. Right Chest x ray at time of discharge from hospital.

patient, the thoracic duct may continue on the right side and enter the veins of the right subclavian region (2).

Thoracic duct injuries that occur in the thorax would therefore usually result in a unilateral right-sided chylothorax. Rare bilateral chylothoraces have been reported following head and neck procedures (3, 8). It is assumed that injury to the thoracic duct in the neck resulted in a leakage of chyle into the superior mediastinum and eventual rupture into the pleura. As in the case reported here, chyle accumulation in the superior mediastinum (chyloma) can present as mediastinal widening (9).

In 1976, Thurer reported a case of bilateral chylothorax occurring two months following the placement of a central venous catheter (10). Venous studies demonstrated bilateral obstruction of the jugulosubclavian confluence, which was believed to be secondary to a chronic mediastinitis. Recently, 5 newborns who developed bilateral chylothoraces shortly after central venous catheterization were reported (11). The bilateral effusions occurred irrespective of the side of the catheter placement. There was no evidence of venous perforation, and in 4 cases venograms demonstrated brachiocephalic and superior vena caval thrombosis. The authors believed the thromboses were extensive enough to obstruct intrathoracic lymph flow.

Thus, chylothorax could occur secondary to thoracic duct flow obstruction or laceration with resultant leakage of chyle into the surrounding tissues. In our case of bilateral chylothorax following a right subclavian central venous catheterization, venous return obstruction due to thrombosis was unlikely. Rather, traumatic damage to the thoracic duct with subsequent infiltration of chyle into the mediastinum and leakage into the pleural cavity is more likely, as in the bilateral chylothorax reported in the radical neck dissection (3). First, the effusions appeared rapidly after the catheter placement, and there was no evidence for venous obstruction (no edema or swelling of the upper extremities). It is well documented that right-sided subclavian procedures may disrupt lymphatic drainage (12). Moosman, in a review of subclavian vein catheterization, states that placement of the needle above or behind the vein, or by penetration of both its walls, can injure the lymphatic ducts with soft tissue lymphedema (12). In addition, our patient's x-ray disclosed a progressively enlarging upper mediastinum (Fig. 1) that resolved after the chyle drainage had ceased.

The diagnosis of chylothorax, once suspected, is usually straightforward. Lipoprotein studies (high triglycerides and low cholesterol), low glucose, cell counts, and total protein can all be used to characterize the fluid. Other tests, including lipoprotein electrophoresis and lymphangiograms, have also been described as useful in difficult cases or when surgical intervention is contemplated (1, 2, 6, 13–16). In patients receiving total parenteral nutrition that includes fat emulsion, as in the case presented, chylothorax may be misdiagnosed as extravasated alimentation fluid. Here, lipoprotein analysis and the glucose level can be utilized to help make the correct diagnosis.

The major consequence of chylothorax is nutritional depletion due to the large amounts of fluid, electrolyte, and protein losses (1, 2, 6). Furthermore, the large lymphocyte loss may compromise the immune system (2). The initial management of chylothorax, regardless of the etiology, is to maintain adequate nutrition, reduce the rate of chyle formation, and thoracostomy tube drainage if dyspnea is present. Traumatic chylothorax is most frequently treated conservatively and most will spontaneously resolve in 7 days (2, 4, 13). Persistent leakage can be managed by thoracic duct ligation (4, 13). The reader is referred to several comprehensive reviews on the treatment of chylothorax (1, 2, 4–7, 13).

Although this case documents the first reported case of acute bilateral chylothorax occurring in an adult following subclavian catheterization, it might be suspected that the incidence of this complication will increase, due both to increased awareness of its occurrence and to an increase in the number of subclavian procedures.

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Retroperitoneal Malignant Fibrous Histiocytoma: Case Report and Literature Review

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Abstract

Retroperitoneal malignant fibrous histiocytoma is a mesenchymal tumor of variant histology characterized by the presence of bizarre histiocytes and giant cells intermingled with fibroblasts arranged in a storiform pattern. Malignant fibrous histiocytoma is a rare tumor occurring in the retroperitoneum in 14% of the cases. Only 16 single cases of malignant fibrous histiocytoma have been reported. We report an additional case and review the literature. Prognosis is usually bad; average survival is 2 years after diagnosis. The 5-year survival rate is 14%. The majority of patients develop pulmonary lesions. The best approach to treatment is wide surgical excision; chemotherapy and radiotherapy provide little help.

Malignant fibrous histiocytoma of the retroperitoneum is an uncommon tumor; only a few cases have been reported. It is a sarcoma that commonly occurs in the deep soft tissues. The lesion is formed by malignant oval and spindle cells, the latter characteristically arranged in the so-called storiform or cartwheel pattern (Fig. 1). Foam cells, malignant giant cells, and pleomorphic fibroblastic cells, as well as variable numbers of inflammatory cells, are also present (Fig. 2). Mitotic figures are usually numerous (Fig. 1). The origin of the tumor is debatable. Based on tissue culture and electron microscopic studies (1–3), a histiocytic origin has been proposed. Some investigators have suggested origination from a primitive mesenchymal cell. In a study of four cases of malignant fibrous histiocytoma, Fu and associates (4) found fibroblastlike, histiocytelike, and undifferentiated cells, suggesting that the undifferentiated cells could give rise to both fibroblastic and histiocytic cells.

Case Report. A 59-year-old man consulted us for weight loss, nausea, and anorexia with a feeling of lightheadedness, without fever or chills. He reported abdominal pain and increased frequency of bowel movements with well-formed stools.

On examination, the patient's blood pressure was 140/80 and temperature was 99.0°F. Lung ascultation disclosed bibasilar rales bilaterally. An abdominal examination revealed a liver span of 14 cm about four fingerbreadths below the right costal margin. An abdominal sonogram exhibited a markedly enlarged liver, and the right renal collecting system was somewhat dilated, which was thought to be caused by obstructive uropathy. An intravenous pyelogram (Fig. 3) showed an irregular calcification in the right psoas muscle at L3–L4, causing a ureteral stricture. Retrograde pyelogram (Figs. 4, 5) demonstrated a ureteral stricture at about 10 cm proximal to the orifice on the right side with right hydronephrosis. The ureteral catheter could not be advanced beyond this level. Pelvic and caliceal dilatation was noted proximally. A computerized tomographic scan displayed a calcified mass of the anterior lower psoas muscle partially obstructing the right ureter. An angiogram (Fig. 6) showed a relatively avascular mass on the right

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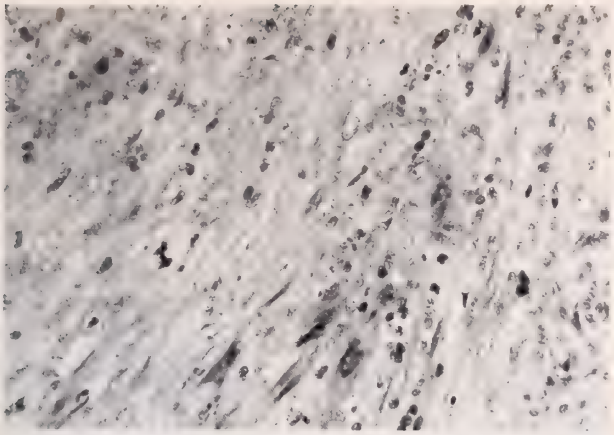


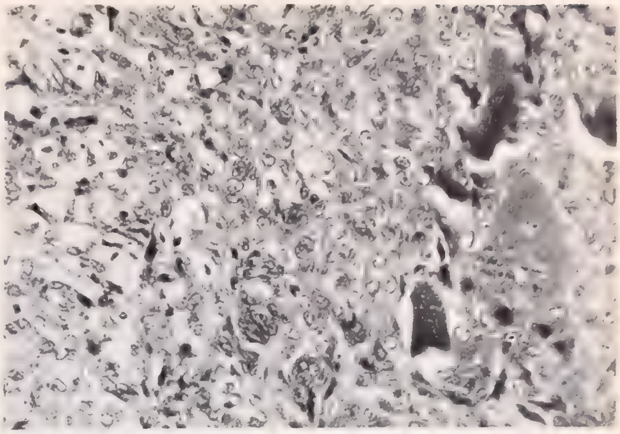


Fig. 1. Left Photomicrograph of storiform pattern in malignant fibrous histiocytoma. Note mitoses (×390 original magnification).

Fig. 2. Right Photomicrograph of giant cells and foamy histiocytes in one microscopic field of a malignant fibrous histiocytoma (×390 original magnification).

side at L3–L4 with marginal corkscrew vessels. A skinny-needle biopsy from that area disclosed fragments of malignant fibrous histiocytoma.

Exploration of the right peritoneum was performed, and the mass was excised with a wide margin, along with a right nephroureterectomy. One week after surgery, the patient was started on a course of radiotherapy to the involved area and received 6,000 rads. The patient was discharged.

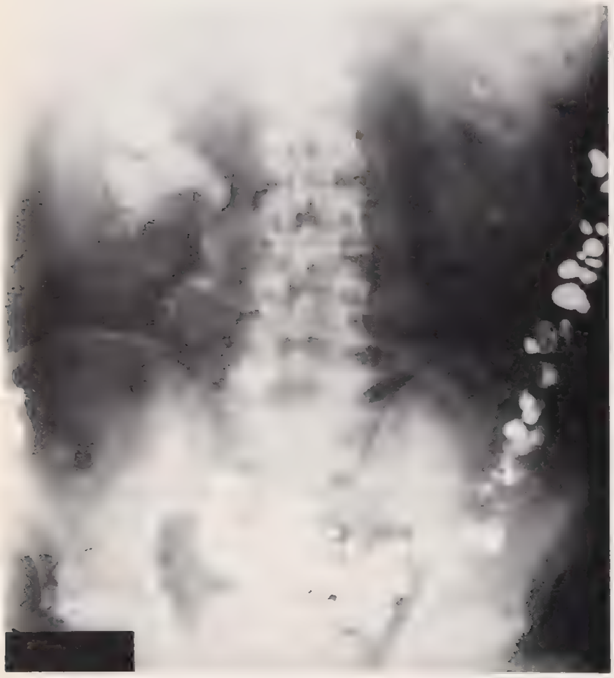
He was readmitted 11 months later with abdominal pain, nausea, and vomiting. At this time, ultrasound studies disclosed a recurrence of the disease locally. Chemotherapy could not be given because the patient had a low ejection fraction on a gated-pool study. The patient was treated symptomatically and discharged. A follow-up complete blood count revealed marked anemia, and the patient was readmitted after 6 weeks because he needed 2 units of packed cells every 2 weeks. Fourteen months after diagnosis, pulmonary metastases were discovered on a chest x ray. At that time, the patient had severe dyspnea at half block, and the decision was made to give the patient chemotherapy. A course of Cytoxan, Oncovin, and actinomycin D was started, but the patient deteriorated rather quickly and died within 2 years of the date of original diagnosis.

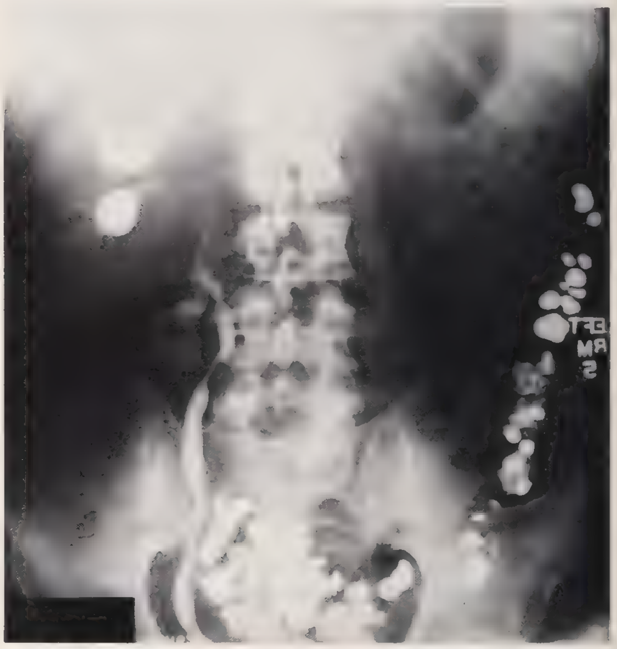
Discussion

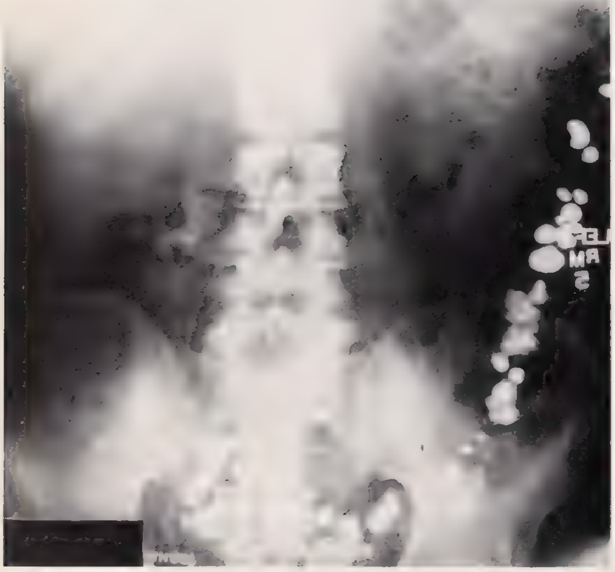
Malignant fibrous histiocytomas are tumors of mesenchymal origin characteristically composed of fibroblastic and histiocytic components (Figs. 1, 2). Most such tumors are localized within the soft tissues of the trunk or extremities, and only 14% occur initially in the retroperitoneum (5). Histologically, the tumor is composed of a fibroblastic component exhibiting a storiform arrangement, and a histiocytic component with giant cells. By light microscopy, both the histiocytes and giant cells contain numerous PAS-positive droplets of different sizes. Electron microscopic examination of these droplets identifies them as irregularly formed, partly fragmented particles having a matrix of different electron density (4). They perfectly resemble disintegration products of red blood cells that occur during erythrophagocytosis and, therefore, can be considered as erythrophagosomes.

Malignant fibrous histiocytoma is noted for its pleomorphic histiologic appearance. On the basis of the criteria suggested by Kempson and Kyriakos (6, 7) and Weiss and Enzinger (8, 9), all tumors can be classed as fibrous, giant cell, myxoid, or inflammatory variants. The fibrous variant is characterized by spindle cells, predominance of fibrocytogenesis, and focal areas with a storiform arrangement. Histiocyte and single or multinucleated giant cells may be found. Mitotic figures are frequent. The myxoid variant has large areas that are relatively hypocellular with widely spaced spindle and stellate cells in a myxoid matrix. The predominant feature of the giant cell variant is a mixture of benign and malignant multinucleated giant cells and, in particular, osteoclastic-type giant cells. The inflammatory variant is characterized by a conspicuous number of neutrophils, plasma cells, lymphocytes, and, in some instances, foam cells.

The symptoms of these tumors vary. However, according to Kearney et al (5), 85% of the patients noted a mass, 20% had pain in the area of the mass, and 10% had referred or poorly localized pain. The retroperitoneal tumors are often associated with fever, fatigue, and loss of weight or gastrointestinal symptoms, as in the patient reported on here. Burgener and Landman (10) were the first radiologists to describe the angiographic features of malignant fibrous histiocytoma. The tumor looked hypovascular, usually well demarcated, and demonstrated fine, cork-







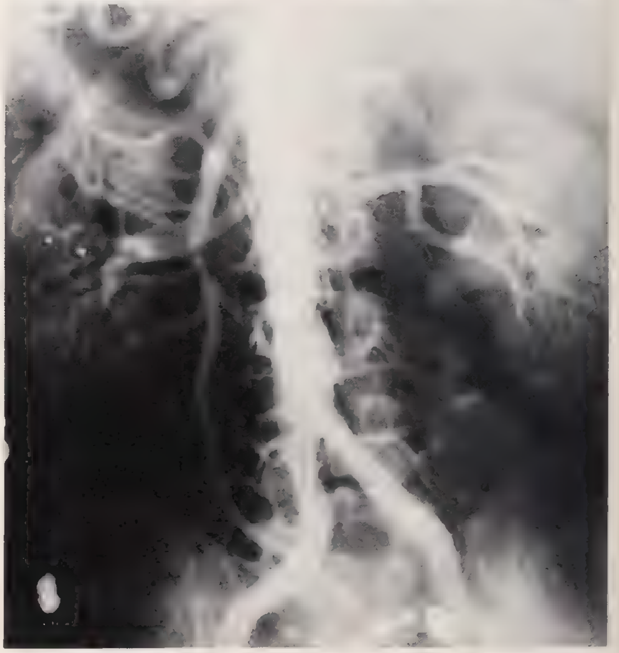


Fig. 3. Top left X ray of intravenous pyelogram showing right hydronephrosis with caliceal dilatation; a mass at L3–L4 impinges on right ureter, producing stricture.

Fig. 4. Top right X ray of bulb retrograde pyelogram showing ureteral stricture at L3–L4 because mass partially obstructs right ureter.

Fig. 5. Bottom left X ray of retrograde pyelogram showing mass at L3–L4 with right ureteral catheter advanced as far as it could be.

Fig. 6. Bottom right X ray of angiogram showing mass on right side (left side of figure) at L3–L4. Mass looks hypovascular, well-circumscribed, with tiny, corkscrewlike tumor vessels.

screwlike tumor vessels with delayed emptying but no tumor blush or early draining veins. The tumor is slightly more common in men and more common after the fifth decade. Distant metastases are most commonly pulmonary. O'Brien and Stout (11) suggested that malignant fibrous histiocytoma could only be diagnosed in the presence of pulmonary metastases. The tendency toward local recurrence or metastatic formation often does not correlate with its biologic appearance. Neither the number of mitoses nor the cellular atypia can be taken singly as reliable criteria for defining malignancy (11, 12).

As far as treatment is concerned, the consensus of opinion is that wide surgical excision, preferably en bloc excision, of the tumor represents the best approach and results in the longest survival. Chemotherapy prolonged the survival in only 33% of the cases (5). Radiation therapy was helpful in destroying metastatic foci, mainly in the lungs and less often in local recurrence (13). A variety of empirical factors—including old age, large size of the tumor, distinct storiform pattern and infiltrative growth, tumor necrosis, and the presence of intense polymorphonuclear infiltrate without tumor necrosis—have proven to be useful in determining a bad prognosis (6, 7, 9, 12, 14). The 5-year survival for patients with retroperitoneal malignant fibrous histiocytoma is 14%.

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Colonic Carcinoma in an Inguinal Hernia Sac: Case Report and Review of the Literature

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Abstract

The association of colon cancer and inguinal hernia has long been debated (1–4), but the occurrence of colonic carcinoma inside an inguinal hernia sac has only rarely been reported. We describe the twelfth such case, which was also complicated by strangulation and perforation.

Case Report. An 80-year-old man was admitted to Elmhurst General Hospital after an episode of hematemesis. He reported intermittent abdominal pain and melena for the previous two months. The medical history was significant for use of nonsteroidal antiinflammatory drugs for arthritis, atherosclerotic heart disease, and a left inguinal hernia for 20 years.

Physical examination showed atrial fibrillation with a ventricular rate of 110 and orthostatic hypotension secondary to blood loss. The abdominal examination revealed a 10-cm irreducible, nontender left inguinal hernia. The hemoglobin was 6.2 g/dl and the hematocrit 19%. After volume replacement and blood transfusion, gastroduodenoscopy showed a large duodenal ulcer with a fresh clot without active bleeding.

On the fourth hospital day, the patient rebled; at this point he had required a total of 14 units of blood since admission. He underwent suture ligation of the gastroduodenal artery, vagotomy, and pyloroplasty. On the eighth postoperative day, the left inguinal hernia became strangulated and perforated into the scrotal sac. The patient underwent a sigmoid resection with a transverse colostomy and mucus fistula and also a left orchiectomy. The colonic specimen (Fig.) contained a lobulated, irregular, oval mass measuring 9 × 8 cm, which histologically was a moderately well-differentiated adenocarcinoma invading the pericolonic fat. The postoperative course was complicated by aspiration pneumonia, enterococcal sepsis, candidemia, and respiratory failure. The patient died on the seventy-third hospital day.

Discussion. Several series and sporadic case reports have associated colonic carcinomas with inguinal hernias (1, 4–9). Increased intraabdominal pressure by asymptomatic partial obstruction of the colon was postulated as the precipitating cause for the hernias (4). Routine preoperative investigation of the colon was, therefore, recommended prior to elective inguinal hernia repair (1, 4, 9). Subsequent studies failed to confirm this association and concluded that routine sigmoidoscopy and barium enema before inguinal herniorrhaphy were unjustified (3, 10–12). Most authors agree, however, that patients with recently symptomatic hernias or with a high index of suspicion for colonic carcinoma should have preoperative investigation. Recent onset of symptoms and a careful history and physical examination should, therefore, be used

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to guide the extent of preoperative investigation that is indicated for each case (12).

Of the surgically excised hernia sacs, less than 0.4% were found to contain tumors, all of which were metastatic (13). According to a classification by Lejar (14) for primary tumors within hernia sacs, there are both saccular tumors, which directly involve the sac itself or the spermatic cord structures, and intrasaccular tumors, which refer to organs bearing a tumor within the sac. The intrasaccular type includes the more common primary hernia sac tumors such as colonic, mesenteric, appendiceal, and bladder tumors. Roslyn et al (15) reviewed the literature in 1980 and tabulated 23 primary hernia sac tumors. Sixteen of these were intrasaccular, and the remaining 7 were saccular tumors. One case involved a femoral hernia, and 22 involved inguinal hernias.

In review of the world literature, we found 11 cases of colonic carcinomas inside inguinal hernia sacs. Including the case of perforated sigmoid carcinoma, reported here, there are now 12 documented cases of colonic intrasaccular-type carcinomas incarcerated in inguinal hernia sacs (Table). In the case we report here, it is possible that the tumor, lying in close proximity to the hernia, spontaneously entered the hernia sac, giving rise to strangulation and perforation. Alternatively, unintentional intraoperative manipulation or postoperative abdominal distention, exacerbated by the pulmonary complications, may have facilitated strangulation and perforation.

Epidemiologic data suggest a link between colonic transit time and the incidence of colon cancer. Prolonged contact with carcinogens in the fecal stream may predispose the mucosa to malignant transformation (16). Probably—perhaps more plausibly—our case represents the coincidence of two very common diseases. The coexistence of colonic carcinoma within an inguinal hernia, however, is infrequent.

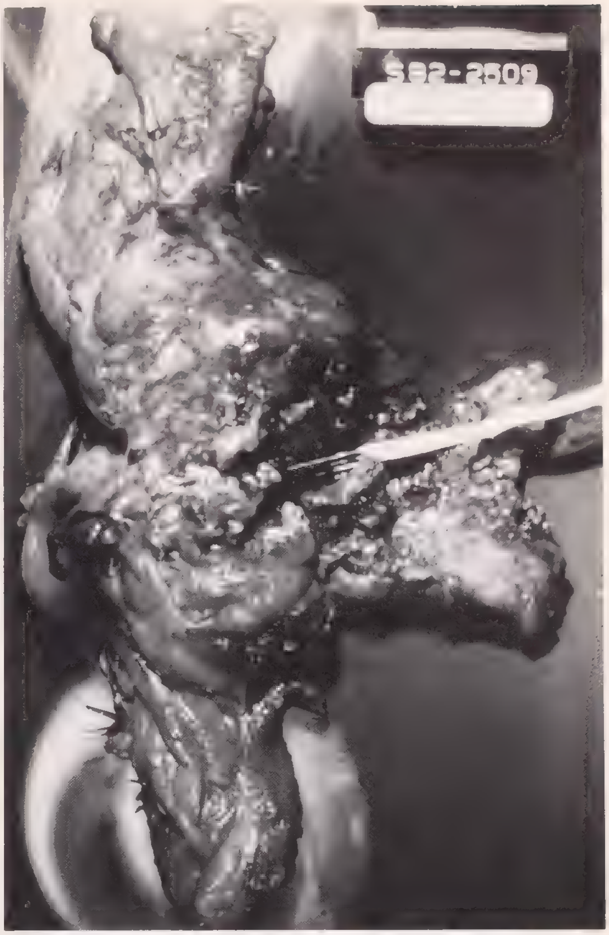

Fig. Serosal view of perforated carcinoma. Probe is through perforation.

TABLE

*Colonic Carcinomas Presenting Inside Inguinal Hernia Sacs**

Author	Year	Age	Sex	Organ	Tumor
1. Gerhardt	1933	37	M	Sigmoid	Carcinoma
2. Fieber	1955	60	M	Sigmoid	Carcinoma
3. Bruce	1958	66	M	Sigmoid	Carcinoma
4. Lookanoff	1960	67	M	Sigmoid	Carcinoma
5. Silberman	1969	62	M	Cecum	Carcinoma
6. Griffiths	1964	74	M	Sigmoid	Carcinoma
7. Dross	1973	76	M	Cecum	Carcinoma
8. Horvath (17)	1974	71	M	Sigmoid	Carcinoma
9. Gross (18)	1980	86	M	Ascending colon	Carcinoma
10. Gross (18)	1980	73	M	Sigmoid	Carcinoma
11. Kanzer (19)	1983	70	M	Sigmoid	Carcinoma
12. Pappas	1983	80	M	Sigmoid	Carcinoma

* Cases 1–7 adapted from Roslyn et al (15).

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Late Diagnosis of Isolated Incomplete Rotation of the Duodenum in a Child

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Abstract

An 8½-year-old boy had severe chronic malnutrition, failure to thrive, abdominal pain, and postprandial bilious vomiting. Evaluation included upper gastrointestinal series and barium enema. Duodenal obstruction of abnormally rotated small bowel was seen in the presence of a complete colonic rotation. At surgery, no volvulus was seen and mesenteric bands that obstructed the distal duodenum were divided. The patient made a satisfactory recovery, free of any abdominal discomfort, with progressive weight gain.

Case Report. An 8½-year-old boy was admitted to the hospital because of recurrent episodes of nausea and postprandial bilious vomiting. These symptoms began in infancy. The patient had been hospitalized when he was a year old for the same reason and had been thought to have viral gastroenteritis. He was seen subsequently with these symptoms by many physicians.

On admission, the patient was mildly dehydrated and malnourished, with weight percentile less than three and height less than five. His abdomen was soft, with no palpable masses and slight epigastric tenderness to deep palpation. Laboratory test results were normal. Intravenous feeding was started. When oral feeding was introduced, abdominal distention accompanied by bilious vomiting and active upper abdomen peristaltic waves developed.

Upright abdominal radiograms showed a few long air fluid levels in the upper abdomen with only a small amount of air in the rest of the bowel, consistent with mechanical proximal small-bowel obstruction. Upper gastrointestinal series demonstrated almost complete obstruction at the level of the distal duodenum. The duodenum was markedly dilated and located to the right of the midline. On a two-hour film, only a little barium was seen to pass into the jejunum. The jejunum was normal in caliber, but was located to the right of the spine (Fig. 1). Barium enema showed a normally rotated colon with the cecum in the right lower quadrant. The diagnosis of obstruction due to abnormal rotation of the duodenum despite a normally rotated colon was made.

Intravenous peripheral hyperalimentation was begun preoperatively. Exploratory laparotomy revealed obstruction of the abnormally fixed duodenum by tight mesenteric bands crossing the duodenojejunal junction (Fig. 2). The colon and cecum were normal in location and fixation. There was no volvulus. The obstructing mesenteric bands were divided. Intraoperative endoscopy showed no mucosal abnormalities or intrinsic obstructive lesion. The patient made an uncomplicated recovery and was discharged two weeks after the surgery, tolerating a regular diet, with subsequent progressive weight gain.

Discussion. Intestinal malrotation manifested as an emergency with midgut volvulus most often occurs in the neonatal period. Abnormalities of intestinal rotation and fixation present a diagnostic problem when found in older children.

These patients suffer from a variety of symptoms, acute and chronic. Acute symptoms

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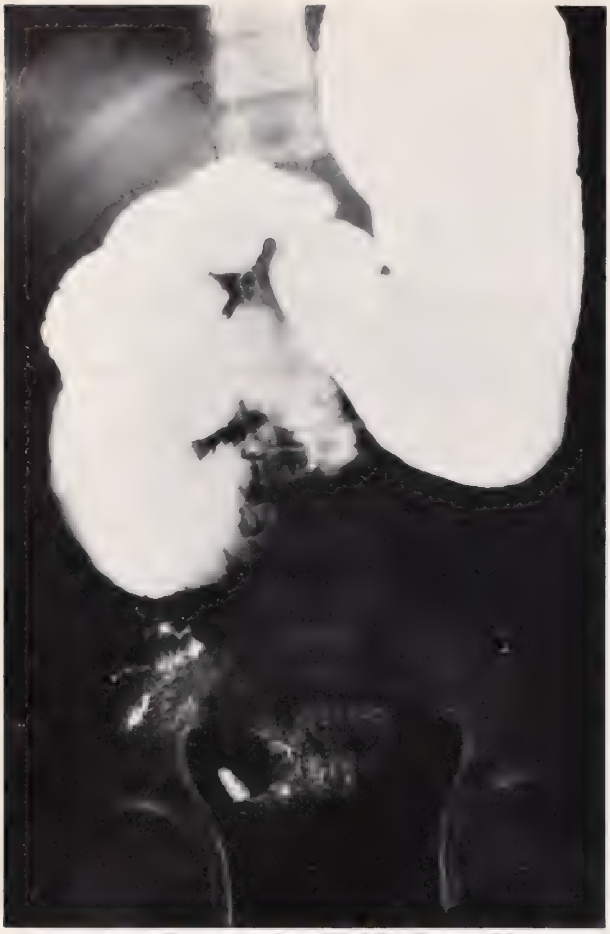

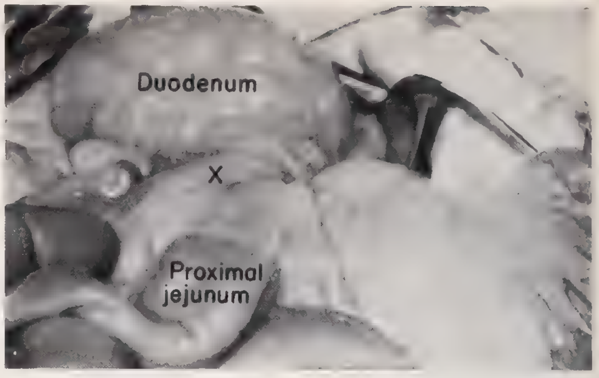

Fig. 1. Left Barium meal and two-hour follow-through reveals the dilated obstructed distal duodenum. The duodenojejunal junction and the barium-filled jejunum are seen on the right side of the abdomen indicating malrotation.

Fig. 2. Right Intraoperative photograph shows dilated duodenum obstructed by abnormal mesenteric bands (X). Proximal jejunum is to the right of the spine.

are related to volvulus and subsequent bowel necrosis, recurrent episodes of abdominal pain, nausea, and vomiting being the chronic ones (1). Eventually, signs of malnutrition and malabsorption can develop, secondary to intermittent bowel and lymphatic obstruction (2).

In older children, the history of recurrent attacks with seeming complete recovery contributes to delay in diagnosis and potentially disastrous complications.

In malrotation, obstructive symptoms have two possible causes. One is from life-threatening volvulus of the midgut, and the other is from obstructing bands which cross the duodenum. Radiographic examination should be performed early in the investigation of these children.

Radiologists have argued over the relative value of the upper gastrointestinal series versus the barium enema as the first diagnostic approach. We advocate the upper gastrointestinal series, and this case gives support for our contention. An entirely normal barium enema with normal position of the cecum does not exclude the possibility of malrotation and volvulus (2, 3).

Malrotation of the intestines is not a single entity but a spectrum of variants. Snyder and Chaffin emphasized that the rotation of the duodenojejunal segment is not completely synchronized with the cecocolic segment. Most of the cecocolic rotation takes place following the return of the bowel from the umbilical sac prior to the tenth week of embryonic life. At that time, the duodenojejunal segment has already completed two-thirds of its rotation (4). When arrest of the rotation of the duodenum occurs, the proximal small bowel is located on the right side of the abdomen with inproper fixation of the mesentery. Adhesive bands crossing the incompletely rotated duodenojejunal junction can cause angulation and obstruction (3, 5). Isolated incomplete rotation of the duodenojejunal segment with normal rotation of the colon has been reported in a small number of patients (6).

The 8½-year-old boy described here suffered from intermittent, long-standing, partial high small-bowel obstruction due to an abnormally rotated duodenum, nearly completely obstructed by tight mesenteric bands.

The usual surgical approach to malrotation is the application of Ladd's principles. Volvulus, when present, is reduced. The duodenojejunal junction is allowed to lie straightened out on the right side of the abdomen. Abnormal bands which cross the duodenum are divided. In the most common type of malrotation, Ladd's bands pass from the cecum, which is in the midabdomen, across the duodenum to the posterior abdominal wall. In our case, however, the cecum was in its normal position. The obstructing bands were adherent to the small-bowel mesentery.

Abdominal pain, vomiting, nausea, and failure to thrive are common in children. When the vomiting is bilious or recurrent, and known to be present for a long time, prompt radiographic evaluation is appropriate to evaluate the cause of the small-bowel obstruction. The findings in this case support the use of the upper gastrointestinal series as the first approach to diagnose malrotation. In this clinical setting, barium enema examination is misleading and not diagnostic.

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Second-Degree Atrioventricular Block and Alpha-Methyldopa: A Probable Connection

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Abstract

We report a case of 2:1 atrioventricular block alternating with Mobitz type 1 second-degree atrioventricular block as a result of alpha-methyldopa administration. This case substantiates clinically that alpha-methyldopa can impair conduction through the atrioventricular node and depress the sinus node. We believe that alpha-methyldopa should be given very cautiously to patients with sinus node dysfunction or atrioventricular nodal disease and to those who may be receiving digitalis glycosides, beta blockers, and calcium channel blockers, which have atrioventricular nodal depressing actions as well. This agent can produce second-degree heart block without the addition of other drugs. We conclude that alpha-methyldopa can further exacerbate and unmask latent disease. It may also be a cofactor in producing the clinical manifestation of atrioventricular nodal disease.

Alpha-methyldopa is known to produce carotid sinus hypersensitivity (1), sinus pause (2), severe symptomatic sinus bradycardia (2, 3), and 2:1 atrioventricular block with proximal block on His bundle study (4). Prolongation of PR interval on the scalar electrocardiogram has also been reported (5). We report a case of 2:1 atrioventricular block alternating with Mobitz type 1 second-degree atrioventricular block as a result of alpha-methyldopa administration. We believe this to be the first case report of Wenckebach disease associated with alpha-methyldopa therapy. The frequency of alpha-methyldopa-induced conduction disturbances is unknown but is probably very low.

Case Report

A 72-year-old black man was admitted July 17, 1984 to the cardiology section with a history of chronic renal failure, nephrectomy for hypernephroma, gout, seizure disorder, and a long history of hypertension. He was originally seen in the renal clinic and found to have a very slow pulse rate with symptoms of weakness and dizziness. He was subsequently admitted to the cardiology section for evaluation and possible pacemaker implantation. At the time of hospitalization, he was receiving alpha-methyldopa, 250 mg. three times a day; phenytoin, 300 mg/day; colchicine, 0.6 mg twice a day; furosemide, 40 mg alternating with 80 mg every other day; lorazepam, 1.0 mg at bedtime; and docusate sodium 100 mg three times a day. He was not taking a digitalis preparation.

The patient complained of having shortness of breath, swelling of his feet, and dizziness for several weeks. His blood pressure on admission was 140/95 and his pulse rate was 22–38 min (Fig. 1). On further questioning, he admitted that on taking his own pulse rate at home, he found it to be in the low thirties the week prior to admission. He did not seek medical attention at that time, although he had been somewhat afraid of going to sleep at night for fear of not waking up because of his slow pulse rate.

In late December 1983, alpha-methyldopa had been prescribed for control of systemic hypertension, and the dose had been increased to 250 mg three times daily. An electrocardiogram done in December 1983 at the start of alpha-

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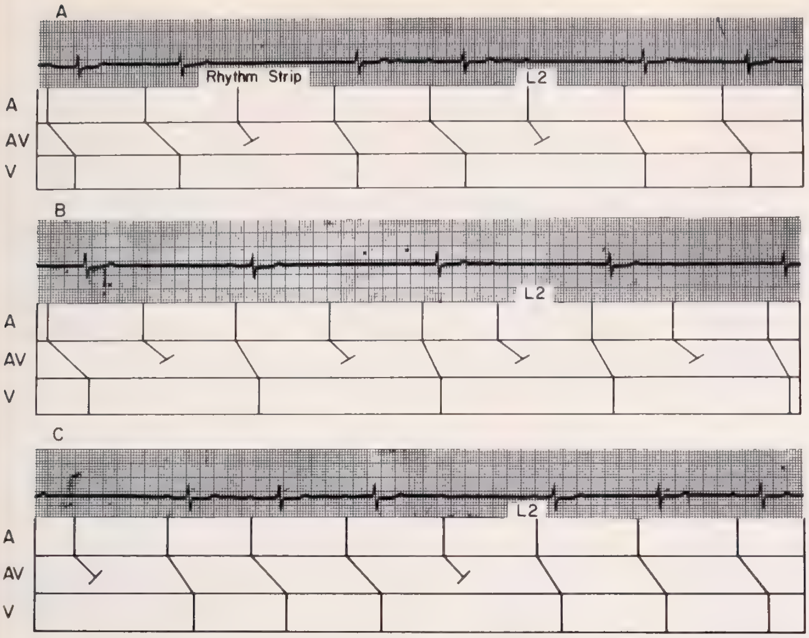
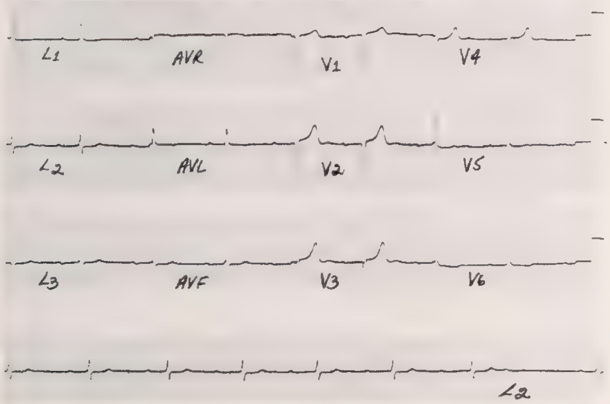


Fig. 1. Mobitz type 1 second-degree atrioventricular block alternating with 2:1 AV block: heart rate 22–38/min. Ladder diagram corresponding to rhythm strip.



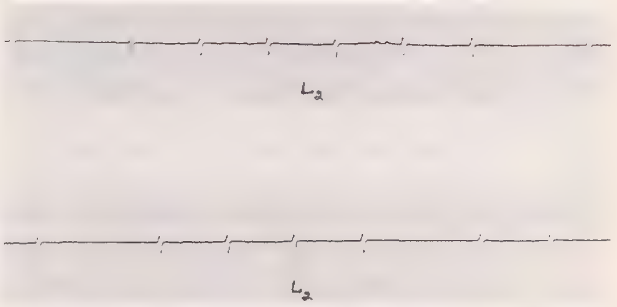
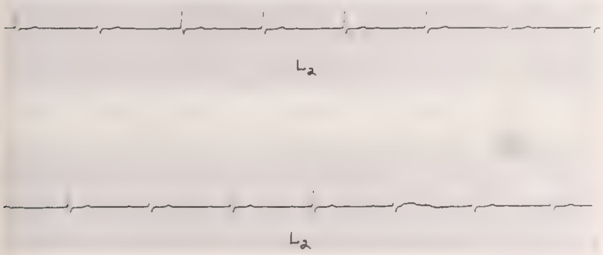
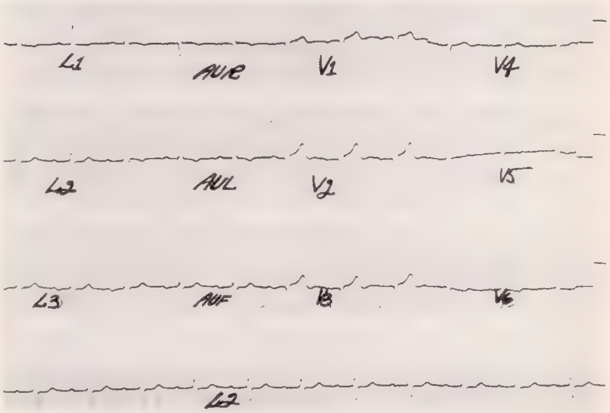


Fig. 2. Left Mobitz type 1 second-degree atrioventricular block. **Above** Rhythm strip, lead 2.

Fig. 3. Below Sinus bradycardia at 40/min with first-degree atrioventricular block (PR interval of 440 msec).
Fig. 4. Right Sinus rhythm at 65/min with first-degree atrioventricular block (PR interval of 320 msec).





methyldopa therapy had revealed normal sinus rhythm at 75/min with PR interval of 200 msec.

After admission, alpha-methyldopa was discontinued without any change in other medications. His atrioventricular conduction gradually improved. Two-to-one atrioventricular block and marked bradycardia (heart rate 22/min) was not seen after the first day of admission. Second-degree atrioventricular block persisted for another 48 hr (Fig. 2). Sinus bradycardia at 40/min with first-degree atrioventricular block (PR interval 440 msec, Fig. 3) was present for an additional 24 hr. On the fourth day after alpha-methyldopa was discontinued, the electrocardiogram revealed near-normal conduction. The rate increased to 65/min, and the PR interval was approximately 320 msec (Fig. 4). The patient refused to be rechallenged or to have a His bundle study.

Discussion

Gould et al demonstrated that alpha-methyldopa can impair conduction through the atrioventricular node and depress the sinus node. Alpha-methyldopa can probably act with other drugs that depress atrioventricular nodal conduction and produce second-degree heart block (4). This patient's second-degree heart block was probably due to alpha-methyldopa because change in its use alone without any other alteration in other medications led to near normalization of conduction. This case fulfills the criteria for the clinical concept of "contributory cause" (6), establishing alpha-methyldopa as a cause of second-degree atrioventricular block. The patient's blood pressure is currently well controlled on prazosin, and his heart rate remains in the sixties with a prolonged PR interval of 320 msec 6 months later.

This case substantiates clinically what Gould et al described earlier after studying the electrophysiologic properties of alpha-methyldopa. The functional refractory period and effective refractory period of the atrioventricular node increased after alpha-methyldopa administration. There was no significant change in the PA and HV intervals (4). We believe that alpha-methyldopa should be given very cautiously to patients with sinus node dysfunction or atrioventricular nodal disease and to those who may be receiving digitalis glycosides, beta blockers, and calcium channel blockers which have atrioventricular nodal depressing actions as well. Alpha-methyldopa can produce second-degree heart block without the addition of other drugs (4). We conclude that alpha-methyldopa can further exacerbate and unmask latent disease. It may also be a cofactor in producing the clinical manifestation of atrioventricular nodal disease.

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Persistent Left Superior Vena Cava: Case Report and Review

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Persistent left superior vena cava is a relatively rare vascular abnormality with an embryologic basis. A patient with this anomaly, unknown at the time of admission, is presented.

Case Report. An 86-year-old man was admitted to The Mount Sinai Hospital for evaluation and treatment of bilateral lower-extremity vascular disease. No medical history could be taken because of language differences and the patient's altered mental status. Physical examination revealed a pacemaker unit subcutaneously in the anterior chest wall. The patient had bilateral rales and 1+ popliteal pulses bilaterally with absent pulses distally. Both lower extremities exhibited 3+ pitting edema and multiple chronic ulcers. Chest x ray showed cardiomegaly, bilateral effusions, and a left-side pacemaker, its lead taking an aberrant route to the region of the right ventricle (Fig. 1). Electrocardiogram showed regular paced beats.

The patient did not respond to three weeks of conservative treatment and died of cardiac arrest immediately following the completion of bilateral below-the-knee amputations.

Discussion. Left superior vena cava (LSVC) is among the most common of venous anomalies, occurring in approximately 0.5% of the general population. Among all patients with congenital heart disease the incidence is 2–3%; among those with visceral or cardiac situs abnormalities the incidence is as high as 40% (1–3). Campbell and Deuchar provided a thorough review of the embryologic basis for this anomaly (4). The condition develops as a consequence of failure of the left anterior cardinal vein to regress. The resultant LSVC usually drains into a dilated coronary sinus, which in turn communicates with the right atrium. If developmental arrest occurs at an earlier time, the coronary sinus will be absent and the LSVC will drain directly into the left atrium, producing shunt disturbances (2, 5). When persistent LSVC is viewed as a sequela of premature arrest of development, it is clear why any patient with other congenital cardiovascular anomalies would be at increased risk for this condition.

Left superior vena cava is most often discovered during surgical repair of congenital heart disorders or secondary to complications during Swan-Ganz monitoring or pacemaker lead placement. The typical route of the aberrant vessel is shown (Fig. 1). On frontal view the lead wire passes inferiorly along the left border of the mediastinum within the LSVC. At the level of the cardiac base it crosses the midline obliquely via the coronary sinus. As the wire emerges from the opening of the coronary sinus into the right atrium, it makes an acute bend. Most frequently this is the point beyond which catheters and lead wires cannot be manipulated (6–8). On lateral view the wire passes caudad at a more posterior level than usual before turning anteriorly to enter the coronary sinus and the right atrium. Suspicion of LSVC should also arise if a widened mediastinum or mediastinal mass is detected. This finding is due to the soft-tissue density of the anomalous vessel found in conjunction with its normal right-sided counterpart. Should observation of a widened mediastinum lead to computerized-tomographic evaluation of the chest (Fig. 2), the LSVC may be interpreted as an enhancing mass lesion (5, 9). Physical examination is unremarkable except in patients having abnormal jugular pulsations.

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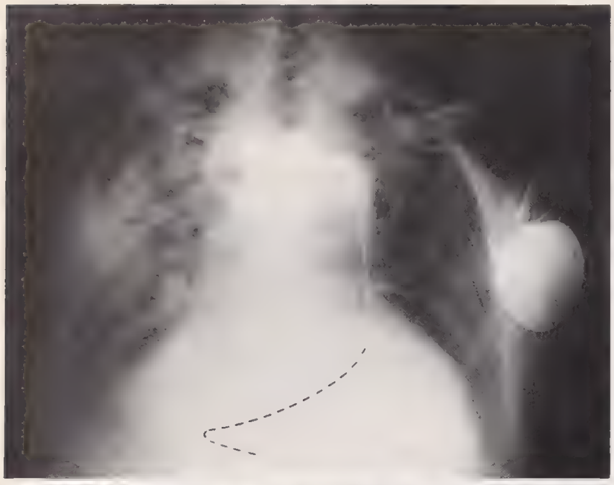

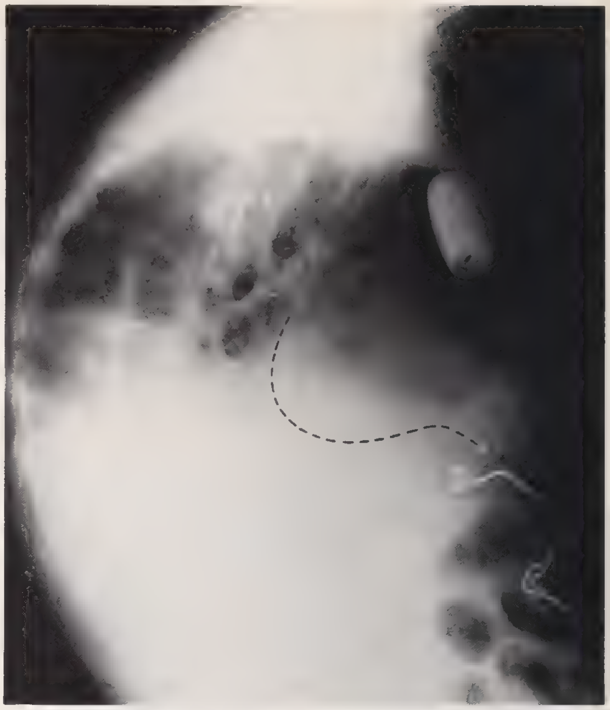

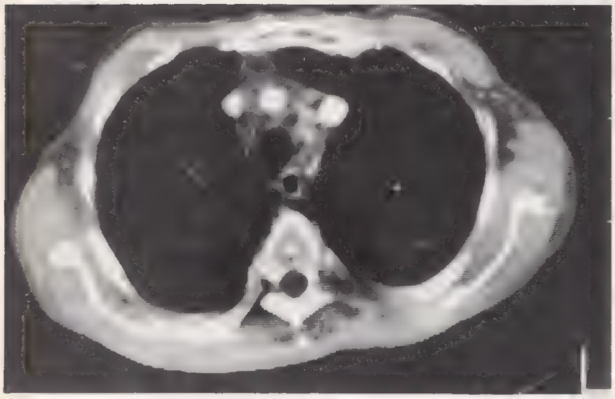

Fig. 1. Left superior vena cava. **Above left** Frontal view. **Above** Lateral view.
Fig. 2. CT scan of left superior vena cava.

Echocardiography reveals a large, retrocardiac, echo-free space representing a dilated coronary sinus, which must be differentiated from a pericardial effusion. Angiographic visualization of the left subclavian or brachial vein will opacify the LSVC, and angiography of the left atrium will demonstrate notching of its inferior border by the dilated coronary sinus (7). The electrocardiogram in these patients shows a typical coronary sinus rhythm with P-wave changes in leads I, II, and III (2, 10, 11). Related to other cardiac abnormalities is the frequent occurrence of sinoatrial node pathology with rhythm and conduction disturbances, necessitating permanent transvenous or epicardial pacing (6, 12). There is a 38% incidence of supraventricular tachycardia and other arrhythmias during invasive monitoring or pacemaker lead placement. This frequency is in part due to the accidental catheterization of the dilated coronary sinus that may occur even if the right superior vena caval route is used. Chest pain, electrocardiographic changes resembling those found with myocardial infarction, and excessive vagal stimulation may result (3, 6).

Summary. Persistent left superior vena cava, among the most common of venous anomalies, is important to recognize and document. It has a significant association with rhythm disturbances and other congenital cardiovascular anomalies. Cardiac surgery, invasive monitoring, and pacemaker placement may be complicated by the presence of this vessel. Specific radiographic and electrocardiographic findings occur with LSVC. Correct interpretation of these findings promotes more efficacious diagnostic evaluation. Invasive procedures should be performed on patients having LSVC with the understanding that they are at increased risk for induced arrhythmias.

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Sexually Transmitted Ocular Disorders Associated with Male Homosexuality

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Abstract

Male homosexuals are susceptible to a variety of sexually transmitted diseases, including gonorrhea, syphilis, and acquired immune deficiency syndrome (AIDS) with opportunistic infections and Kaposi's sarcoma. A number of these conditions may produce characteristic ocular manifestations, commonly cotton-wool spots with or without retinal hemorrhages, cytomegalovirus retinitis, and conjunctival and adnexal Kaposi's sarcoma. Familiarity with these ocular signs and a careful ophthalmologic examination may aid in the early diagnosis of many of these conditions.

Homosexual males, particularly those with more than one sexual partner, are at high risk for infection with common sexually transmitted pathogens (*Neisseria gonorrhoeae, Treponema pallidum,* cytomegalovirus, and hepatitis A and B). This increased risk is thought to be a function of promiscuity, direct oral-anal contact, and the practice of fellatio and anal intercourse. In the U.S., homosexual and bisexual males constitute 80% of all cases of acquired immune deficiency syndrome (AIDS). The remainder have occurred in heterosexual males and females, most of whom were drug abusers. The prominent ocular manifestations of gonorrhea, syphilis, and AIDS are discussed.

Gonorrhea

In the United States, gonorrhea has become pandemic. It is most commonly reported among poor, unmarried, sexually active persons living in large cities. In homosexual men the primary source of spread is from symptomatic urethral and anorectal infections, but most such infections are asymptomatic. Pharyngeal gonococcal infection is common in gay men but is not usually a source of transmission (1–3).

Gonococcal ophthalmia is a well-known and severe manifestation of this disease. Adult gonococcal conjunctivitis is probably the result of direct contamination with infected genital secretions from a sexual partner. Hematogenous spread has also been implicated (4). The average incubation period is 3 days. Initially, a watery discharge is present, which quickly progresses to thick, purulent discharge. Lids and conjunctivae may appear injected and edematous. The untreated eye progresses rapidly to the more serious sequelae of corneal ulceration and perforation (Fig. 1). Endophthalmitis and panophthalmitis may also result. The visual prognosis depends on the extent of corneal involvement and the immediacy with which treatment is initiated. Since *N. gonorrhoeae* is one of the few organisms that can penetrate the intact corneal epithelium, rapid diagnosis as well as prompt and effective therapy within 24 hr is necessary to prevent corneal perforation. Gonococcal conjunctivitis should be suspected in any purulent conjunctivitis. Gram stain demonstrating gram-negative intracellular and extracellular diplococci is presumptively diagnostic, and treatment should be started even before culture results are available (Fig. 2).

Recommended Treatment. Aqueous penicillin G, 10 million units/day, is given intravenously, until the active infection is arrested (minimum of 7 days), followed by ampicillin, 500 mg orally

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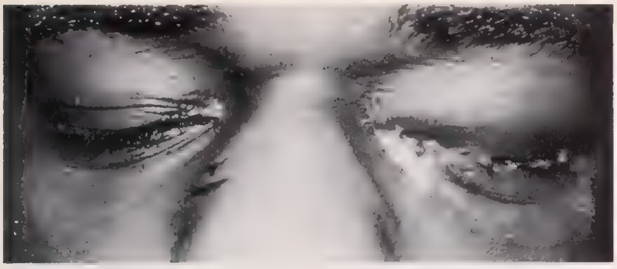


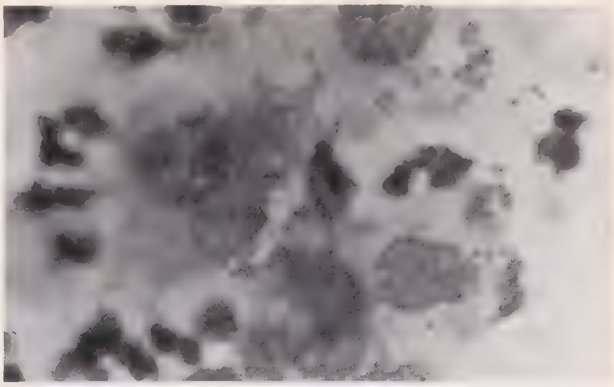


Fig. 1. Patient with purulent ocular discharge and erythematous lid. Gonococcal conjunctivitis can progress to corneal ulceration and perforation if untreated.

Fig. 2. Gram stain of gonococcal conjunctivitis demonstrates gram-negative intracellular and extracellular diplococci.

four times daily for at least 10 days. Topical therapy should include saline irrigation of the eye followed by tetracycline or bacitracin ointment instilled every 2 hr for the first 2 days, and then 5 times daily until resolution (5).

Syphilis

Syphilis persists worldwide as a highly contagious venereal disease. The epidemiology of syphilis in the United States is changing dramatically, as evidenced by a growing percentage of white homosexual men among all new cases (6, 7). Of men with early syphilis in the United States, 30%–40% are homosexual or bisexual. The association of syphilis and eye disease is well known. The ocular manifestations are protean and, like the systemic forms, depend on the chronological stage of the illness.

In acquired syphilis, ocular manifestations include roseola of the iris, iridocyclitis (early secondary stage), uveitis/vitritis (late tertiary stage), diffuse chorioretinitis, and papillitis (8).

The early roseolae of the iris represent hyperemia of the vascular loops of the iris. They are transient and benign, disappearing within a few days. At a later stage, recurrent roseolae may occur and are associated with exudates, formation of synechiae, and the development of iris papules (9). Gummata of the ciliary body or in the angle are also sequelae of severe syphilis.

Acute iridocyclitis is seen in the secondary and tertiary stages of the disease. In 1931, Moore reported that 4.6% of the patients with early secondary syphilis had uveitis. In recurrent secondary syphilis, which is much rarer, the incidence of uveitis was 9.3% (10). In a more recent series, Schlaegel and Kao reported a 1.1% incidence of presumed syphilitic uveitis over a 10-year period (11).

The iridocyclitis of syphilis may be associated with nodule formation (syphilitic gumma), papular lesions at the pupillary margin, or multiple nodules on the iris surface. Syphilitic chorioretinitis is a primary choroiditis with secondary involvement of the retina (Fig. 3). The choroiditis can be unilateral, bilateral, or diffused in the form of choroidal edema. There is resultant chorioretinal scarring, vascular sclerosis, and pigment migration. The retina may demonstrate the characteristics of pseudoretinitis pigmentosa (12, 13). The vitreous typically shows diffuse yellow haze and multiple yellow-gray exudates. These posterior pole exudates may be perivascular or associated with flame-shaped hemorrhages. Vasoocclusion of the vessels and vasculitis may also be seen (14, 15).

Syphilitic involvement of the central nervous system may be asymptomatic or may take the form of meningitis, meningovasculitis, parenchymatous neurosyphilis, or gummatous neurosyphilis (16–19). Optic neuritis has been reported in secondary syphilis with meningeal involvement (20, 21). Perioptic neuritis, bilateral inflammation of the optic nerve sheaths sparing the optic nerves, has also been reported. Visual acuity is unaffected, but the optic discs are swollen (22, 23).

Diagnosis of syphilis is based on positive serologic tests. The VDRL and rapid plasma reagin agglutination test are the most extensively used means of detecting reaginic antibody. The FTA-ABS (fluorescent treponemal antibody) is more sensitive than the VDRL, and the *T. pallidum* immobilization test is highly specific. Patients with clinical signs of ocular syphilis and neurosyphilis may show negative reactions to blood reagin tests for syphilis. Schlaegel and Kao recently reported that 75% of their syphilitic uveitis patients had negative VDRL tests, but all had a positive FTA-ABS test (11). Microhemagglutination assay based on the ability of trepo-

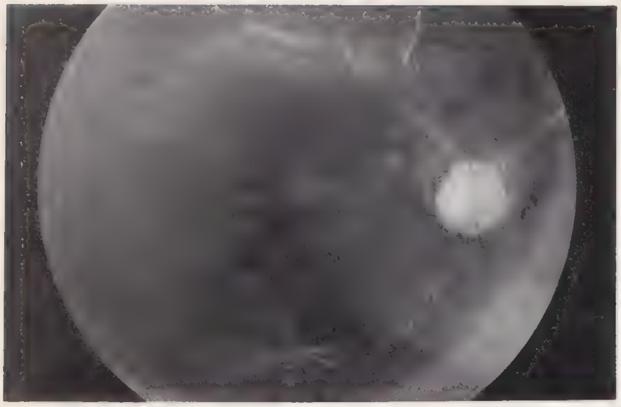


Fig. 3. **Left** Patient with pseudoretinitis pigmentosa; chorioretinal scarring with vascular sclerosis and pigment migration.

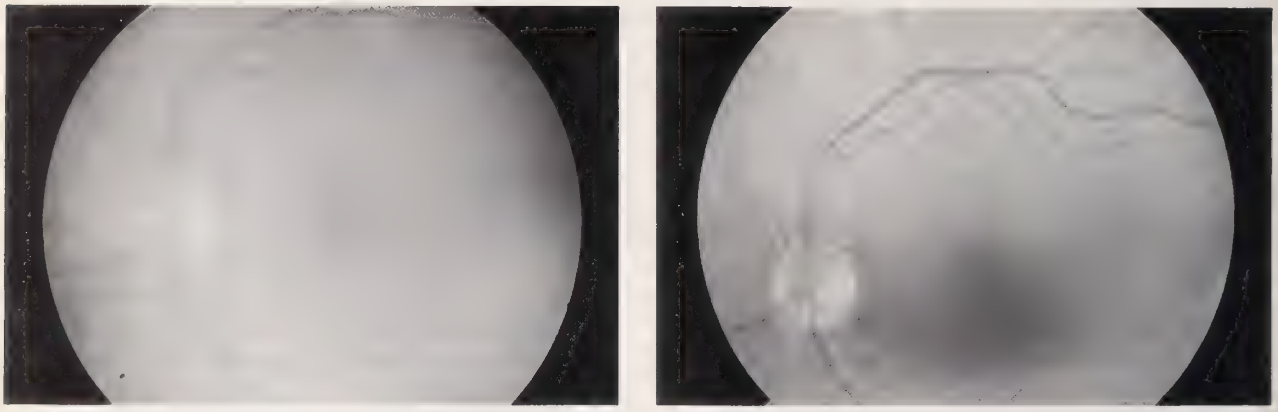


Fig. 4. Patient with 4+ vitritis and visual acuity of hand motions. **Below left** Although VDRL was negative, FTA-ABS was positive. **Below right** Two months after treatment with intramuscular Benzathine penicillin G, visual acuity was 20/25.

nemal antibodies to agglutinate red blood cells coated with *T. pallidum* antigen is being utilized as a confirmatory test.

Examination of cerebrospinal fluid is necessary in patients with suspected syphilitic optic neuritis to confirm the diagnosis and to judge the adequacy of the treatment of choice for all stages of syphilis (24).

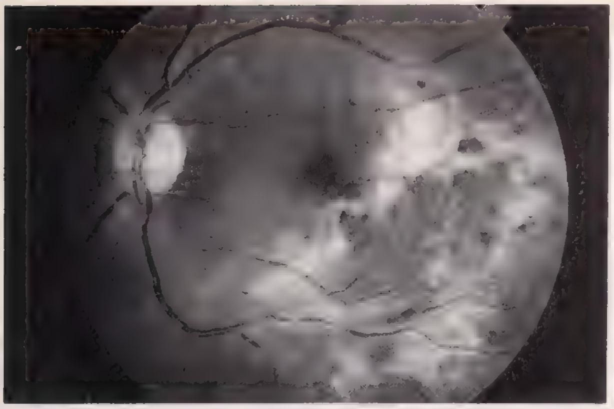
Treatment. Benzathine penicillin G, 2.4 million units intramuscularly, once, followed by 1.2 million units Benzathine penicillin G or 600,000 units of procaine penicillin G daily for 8 days, is recommended for early syphilis (primary, secondary, latent of less than 1-year duration). Two to four million units intravenously of crystalline penicillin G every 4 hr for at least 10 days followed by Benzathine penicillin G, 2.4 million units intramuscularly weekly for 3 weeks, is the preferable therapy for neurosyphilis. The dose for optic perineuritis is not established (25).

The diagnosis of syphilis should be considered in any patient with unexplained pupillary abnormality; unexplained optic neuritis; pseudoretinitis pigmentosa; iritis (anterior uveitis) unresponsive to steroid and mydriatic therapy; any posterior uveitis that does not respond to steroid therapy but persists or worsens (Fig. 4).

AIDS

In the U.S., male homosexuals are among the high-risk groups susceptible to AIDS and account for 80% of all cases. The syndrome is marked by neurologic deficits, a constellation of opportunistic infections (cytomegalovirus, *Pneumocystis carinii, Candida,* toxoplasmosis, aspergillosis, cryptococcosis, among others), and a particularly virulent form of Kaposi's sarcoma. AIDS affects previously healthy individuals (primarily male homosexuals, intravenous drug abusers, hemophiliacs) who are deficient in cell-mediated immunity and have a T-lymphocyte subpopulation imbalance. The etiology of AIDS is thought to be a transmissible blood-borne agent, HTLV-III. The high frequency of sexual activity and multiple sexual partners among some homosexual men may explain the likelihood of exposure through semen or a blood-borne agent. Cytomegalovirus (CMV), to which promiscuous homosexual men are constantly exposed, has been reported to be a possible immunosuppressive agent (26–37).

The opportunistic infections associated with AIDS have ocular as well as systemic manifestations (38). Ocular involvement in CMV is usually



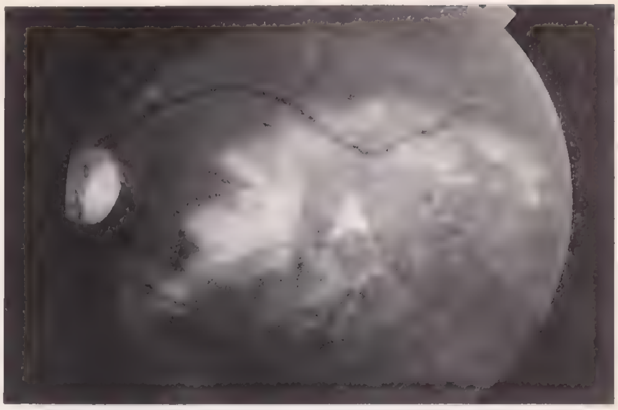
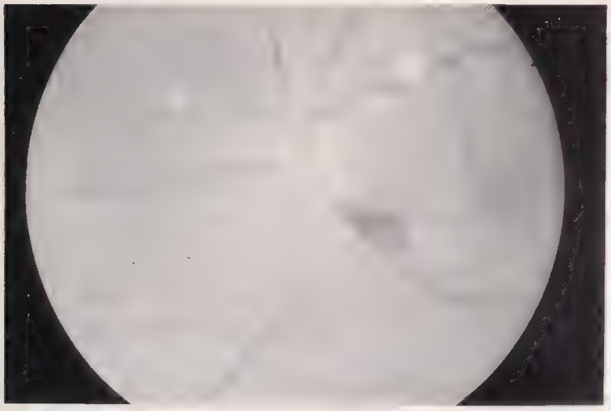


Fig. 5. Left Patient with cytomegalovirus retinitis involving posterior pole but sparing macula. Retina demonstrates area of retinal necrosis and hemorrhage.
Fig. 6. Same patient **Right** 1 month later, when visual acuity was light perception. Entire posterior pole was involved.



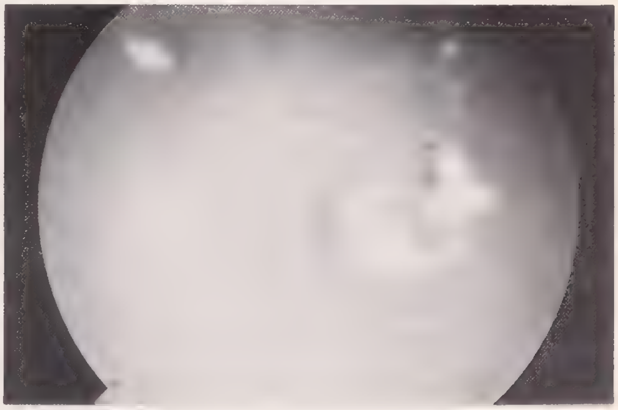
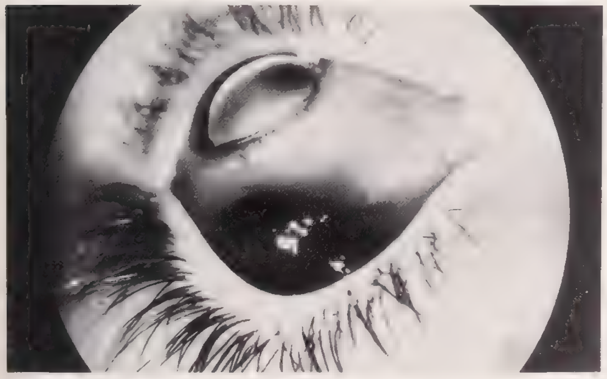


Fig. 7. Left Cotton-wool spots of *Pneumocystis carinii* in patient with *P. carinii* pneumonia proved at biopsy.
Fig. 8. Right Diagnosis of *Candida* endophthalmitis established by vitreous tap in this intravenous drug abuser. Patient was treated with intravitreal and systemic amphotericin.



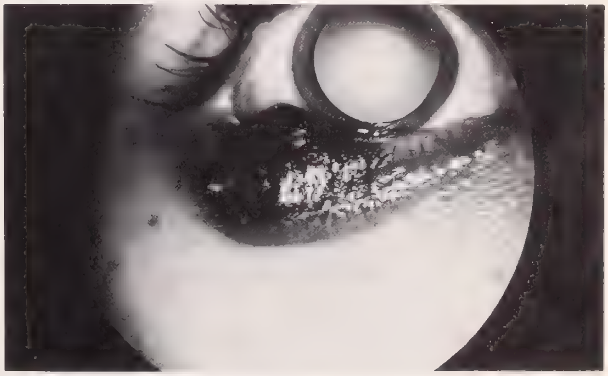


Fig. 9. Left Large red-purple lesion of Kaposi's sarcoma on bulbar conjunctiva, an uncommon site.
Fig. 10. Right Lesion of Kaposi's sarcoma on lid; lesion arose from palpebral conjunctiva.

retinal, producing a characteristic picture of confluent white and granular ("crumbled cheese") lesions, usually associated with hemorrhage (Figs. 5, 6). Atrophic areas of retina necrosis are accompanied by pigment dispersion, vascular sheathing, and optic atrophy. Microaneurysms, retinal edema, exudative detachment, cotton-wool spots, and anterior uveitis can also be seen. The differential diagnosis includes herpes simplex retinitis, toxoplasmosis, fungal retinitis, Behçet's syndrome, and the syndrome of unilateral or bilateral acute retinal necrosis (39–41).

CMV. Active CMV is diagnosed based on elevation of complement-fixation antibodies, positive blood cultures, or a biopsy confirmation (typical intranuclear or intracytoplasmic inclusions). CMV therapy has been unsuccessful. The retinitis of CMV similarly has been poorly responsive to antiviral therapy, including Acyclovir with and without interferon (42). A new antiviral agent, Ganciclovir (Burroughs Wellcome), has been evaluated as possible therapy for CMV retinitis by the authors (JO, AF).

P. carinii. The predominant opportunistic infection in AIDS is *P. carinii* (26, 29, 43, 44). Cotton-wool spots, the major common ocular manifestation of pneumonia associated with *P. carinii* (Fig. 7), are the result of focal ischemia (45). These lesions resemble the spots in diseases associated with circulating immune complexes or microvascular occlusive disease. The spots may on occasion be associated with hemorrhage.

Definitive diagnosis requires demonstration of the organism in the sputum or in material obtained from transtracheal aspiration. Diagnosis may even require an open lung biopsy.

Therapy consists of pentamidine isethionate or trimethoprim sulfamethoxazole in dosages of 20 mg/kg trimethoprim and 100 mg/kg sulfamethoxyazole each 24 hr in equally divided doses for 14 days.

Candida. The retinal lesions of *Candida* are typically small, yellow-white retinal infiltrates. The lesions usually have fluffy borders and range in size, producing vitreous abscesses which may lead to retinal detachment (46) (Fig. 8).

Toxoplasmosis. The initial symptoms of toxoplasmosis may appear in the eye: focal necrotizing retinochoroiditis, perivasculitis, and juxtapapillary lesions resembling optic neuritis. Vitreous opacities and yellow-white intraretinal lesions with irregular borders are characteristic. Resolution of these lesions leaves a pigmented chorioretinal scar. Lesions may produce visual loss if they are located in the macula, papillomacular bundle, or at the optic nerve head. Involvement of a branch retinal artery can produce retinal artery occlusion (46, 47).

Kaposi's Sarcoma. This sarcoma, a heretofore rare angiosarcoma with a predilection for the skin, is usually seen in older men of Jewish and Mediterranean descent. The version that has emerged in the homosexual AIDS population is much more aggressive and progressive than the entity seen in older men. The association of Kaposi's sarcoma and AIDS has been recognized since 1981. CMV has been linked to the pathogenesis of Kaposi's sarcoma in male homosexuals (35). The bluish-purple nodules of the sarcoma usually are seen first on the upper and lower extremities and spread toward the trunk. The visceral organs may also be affected.

Ocular involvement with Kaposi's sarcoma has been uncommon. The conjunctivae are the most frequently involved ocular structures (Fig. 9). Lid, lacrimal sac, and caruncle involvement have also been reported (Fig. 10). The palpebral conjunctivae are affected more often than the bulbar portion. The lesions may take the form of well-circumscribed subepithelial nodular masses or of a more diffuse infiltrative, inflammatory process. These lesions may mimic squamous cell carcinoma, malignant melanoma, or granuloma pyogenicum (48–50).

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Pathology Notes *William Thomas Jr., M.D., editor*

With the exception of renal cell carcinoma and malignant melanoma, endobronchial metastases are very rare. This report records two extremely rare events: primary duodenal carcinoma, and metastases from this tumor to the endobronchi as well as the more common lung parenchymal sites.—WT Jr

Endobronchial Metastatic Carcinoma From an Occult Carcinoma of the Duodenum

SAROJA ILANGOVAN, M.D., MARCELINO G. REYES, M.D., AND SANTOSH MEHTA, M.D.

Abstract

Bronchial biopsies of a 59-year-old man suspected of having bronchogenic carcinoma showed a poorly differentiated adenocarcinoma. At autopsy, three months later, we found an adenocarcinoma of the duodenum with metastases to lymph nodes, pancreas, liver, and the major bronchi and parenchyma of both lungs. We report this case as a reminder that adenocarcinoma of the duodenum can present as endobronchial metastases and mimic the clinical and biopsy findings of bronchogenic carcinoma.

Case Report. A 59-year-old black man was hospitalized because of shortness of breath, cough productive of white sputum, and weight loss of two months' duration. Physical examination revealed decreased breath sounds in both lung fields. Chest radiographs showed a large mass in the left hilum and scattered infiltrates in the adjacent lung and in the right lower lobe (Fig. 1). Bronchoscopic examination revealed that the mucosa of the orifice of the anterior and lateral segments of the bronchi of the left lower lobe was discolored white and lifted above the carina by what was interpreted as neoplastic infiltration. Forceps biopsies of the abnormal bronchial mucosa showed a poorly differentiated adenocarcinoma that did not appear to have a clear transition from adjacent epithelium. He refused further tests and treatment and died of respiratory failure four weeks later. Nine days before he died, he complained of abdominal pain that was relieved by antacids. Although we could not tell from the biopsy if the adenocarcinoma was primary or metastatic, the clinicians felt that he had an adenocarcinoma of the left lung with intrapulmonary metastasis.

At autopsy, we found tumor encasing the major bronchi of both lungs. There was extension into the adjacent lung parenchyma and the overlying pleura (Fig. 2). The hilar and perihilar lymph nodes contained metastatic tumor. In the second part of the duodenum we found an ulcerated neoplasm measuring 1.5 × 2.0 × 0.5 cm. Metastatic tumors were also found in the pancreas, peripancreatic and periaortic lymph nodes, liver, and lumbar vertebrae. Microscopic examination of the duodenal tumor showed a poorly differentiated adenocarcinoma arising from the mucosa (Fig. 3).

Discussion. Although adenocarcinomas of the duodenum make up half of all primary adenocarcinomas of the small bowel, they are nonetheless uncommon because malignancies of the small bowel account for only 1% of all cancers of the gastrointestinal tract (1). Diagnosis is often delayed because symptoms are mild and chronic (2). Thus, in a study by Ouriel and Adams (1), 13 of 32 patients were considered to have unresectable duodenal adenocarcinomas at the time of diagnosis because of metastasis to the liver or the surrounding organs. None had metastasis to the lungs.

Also uncommon is endobronchial metastasis (grossly visible metastasis to the major bronchi). In Braman and Whitcomb's review of 244 patients who died of solid extrapulmonary tumors, only 5 patients (2%) had endobronchial metastasis (3). In those 5 patients and 28 others re-

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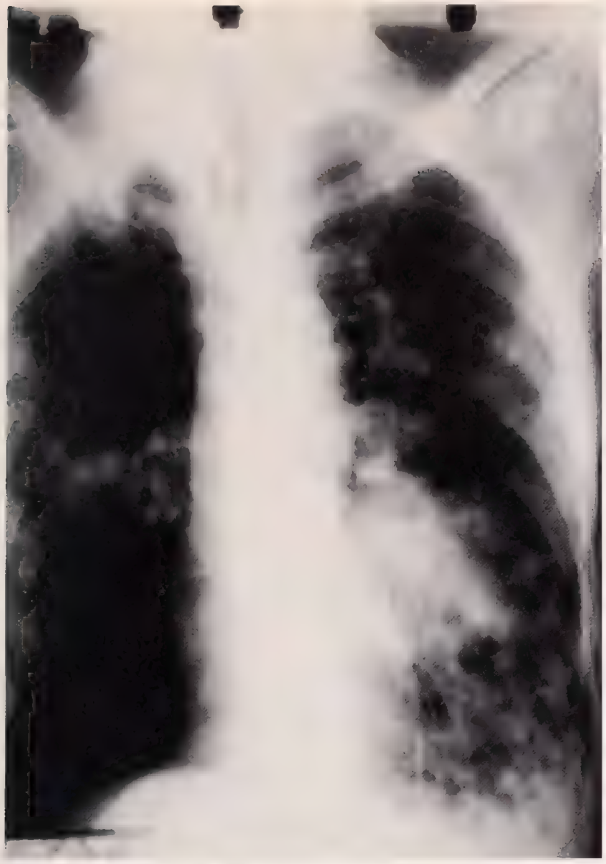

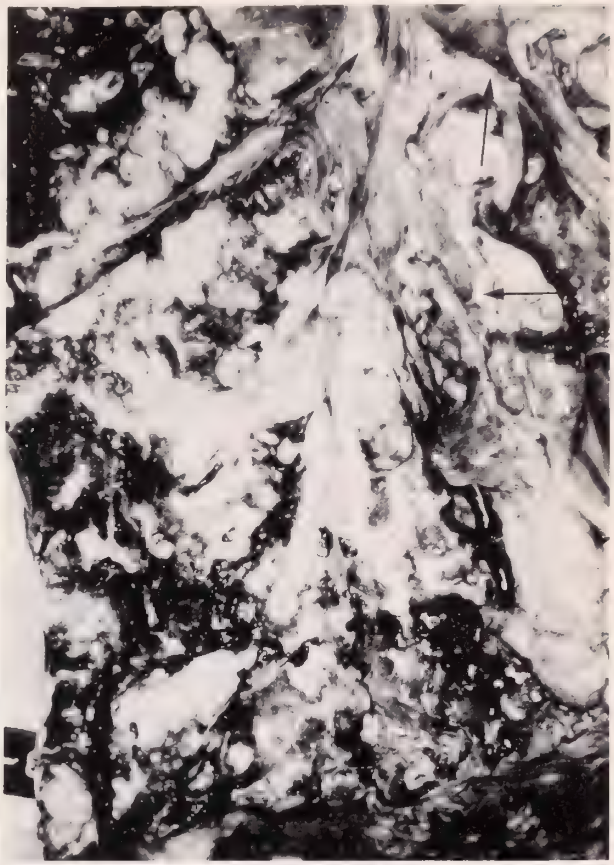

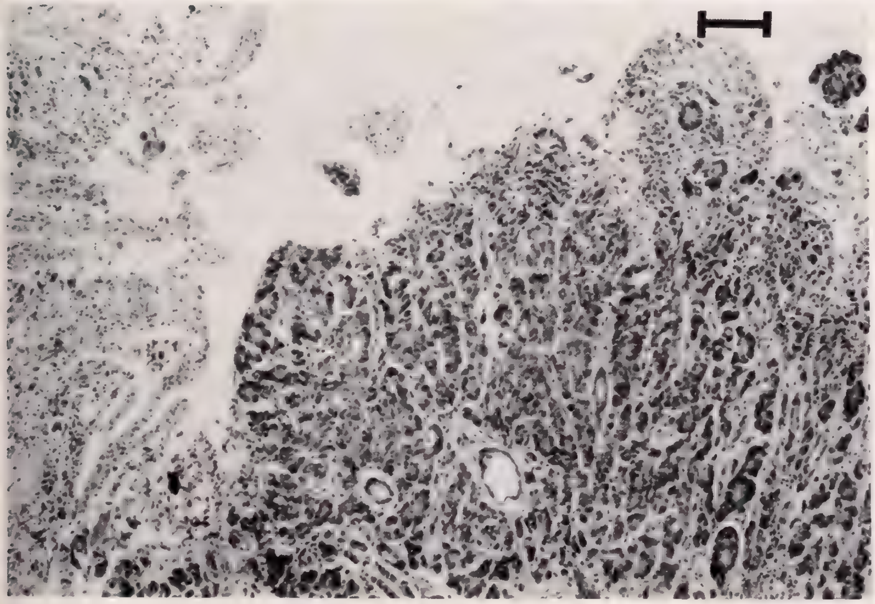

Fig. 1. Top left Chest radiograph showing mass in left lower lobe and multiple densities in both lung fields, which were interpreted as metastatic deposits from mass in left lung.

Fig. 2. Top right Section of left lower lobe of lung through a major bronchus showing metastasis in lumen (arrows) and parenchyma.

Fig. 3. Left Microscopic section of duodenum showing a poorly differentiated adenocarcinoma arising from mucosa. Bar = 500 μm.

ported in the literature, the primary tumor was in the kidneys, colon and rectum, testes, prostate, uterus, adrenals, and skin (melanomas). None were in the small intestine. More important, the authors pointed out that endobronchial metastasis can rarely be confused with bronchogenic carcinoma if, like our patient, the metastasis antedates the primary tumor or if the bronchial biopsy fails to suggest a primary site by the presence of carcinoma in situ of the adjacent bronchial epithelium.

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Psychiatry Notes

Kenneth R. Kaufman, M.D., editor

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Psychiatry is no longer simply a humanistic approach to a troubled patient. To a large extent, analytic theories have given way to the scientific mapping of psychiatric disorders. With the availability of electroencephalograms, computed axial tomography, regional blood flow studies, positron emission tomography, and magnetic resonance imaging, the modern psychiatrist has literally leaped into the forefront of a neuroscience explosion of knowledge and application. Though the many forms of psychotherapy are important to the total care of a psychiatric patient, the specialist should be well versed in psychopharmacology, neurotransmitters, receptor sites, genetics, and the psychiatric implications of medical illnesses.

The purpose of these Notes will be to review biological psychiatric theories; present research studies on psychotropic drug usage, interactions, and complications; and discuss the unusual psychiatric case. Further, this section will be dedicated to emphasizing the role psychiatry can and should play as a subspecialty in medicine.—KRK

Serotonergic Mechanisms Of Lithium Action

Paul J. Goodnick, M.D.

Manic-depressive illness was for centuries a major cause of mental disability. Few treatments were available even to ameliorate the symptoms of mania (increased energy, decreased need for sleep, and grandiosity) and of depression (anorexia, insomnia, and suicidal ideation). Patients at one time died of manic exhaustion and of malnutrition with dehydration. The development of neuroleptics and antidepressants significantly improved the lot of these individuals. However, until lithium was discovered as a treatment for mania in 1949 by Cade, there was no specific treatment for this disorder. The successful application of lithium for treatment of mania was developed in the 1950s in Denmark by Schou and associates. Its use for prevention of recurrences of mania and depression was discovered in the 1960s by Baastrup and associates in Denmark and by Fieve and Gershon in the United States (1).

Lithium is at present well-established as the agent of choice in the treatment of mania, as well as in the prevention of recurrences of bipolar illness (2). It has been used with success in the treatment of schizoaffective disorder (3). The success of lithium in treating the opposite poles—mania and depression—of bipolar disorder has intrigued many investigators searching for the answer to lithium's mechanism of action.

In the third edition of the Diagnostic and Statistical Manual of Mental Disorders of the American Psychiatric Association (1980), manic-depressive illness was relabeled "bipolar affective disorder." Biological research into the causes of depression and mania have now been in progress for twenty-five years. Implicated roles in depression and mania have been discovered for norepinephrine (NE), serotonin (5HT), dopamine (DA), and acetylcholine (Ach). Yet, in terms of the onset of the trait for development of both mania and depression, some of the major hypotheses of affective disorders are based on the presence of abnormalities in serotonin (5HT).

The serotonin-permissive hypothesis states that abnormal serotonin activity leads to a state of vulnerability to onset of either mania or depression (4). Several lines of indirect evidence have at least partially supported this hypothesis. Relevant studies of urinary and cerebrospinal fluid metabolites, platelet indices of serotonin activity, and neuroendocrine challenges are summarized below, while focusing on effects of short-

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TABLE 1
Serotonergic Effects of Lithium Carbonate

Author & year (ref)	Parameter	Population (no.)	Baseline	Treatment	Prophylaxis	Withdrawal
Linnoila 1984 (17)	Urinary 5HT/24 hr (pmole)	Depressed (21)	1100	250	—	—
	Urinary 5HIAA/24 hr (nmole)	Depressed (21)	17.0	13.0	—	—
Rudorfer 1985 (18)	Urinary 5HIAA/24 hr (nmole)	Normal controls (12)	23.4	21.8	—	—
Bowers 1977 (16)	CSF (ng/ml) 5HIAA	Manic (5)	91.8	136.4	—	—
		Depressed, hx mania (6)	129.7	126.5	—	—
		Depressed, no hx mania (5)	87.2	104.6	—	—
		Schizoaffective (5)	122.8	144.0	—	—
		ALL (23)	107.1	130.5	—	—
Berrittini 1985 (19)	CSF (pmol/ml) 5HIAA	Controls (30)	72.3	—	—	—
		Euthymic bipolars (25)	—	—	99.3	92.3

term and long-term lithium treatment. A discussion of the clinical implications of lithium-related findings then follows.

Lithium-Related Findings. The major metabolite of serotonin is 5-hydroxyindolacetic acid (5HIAA). A series of studies have reported cerebrospinal levels of 5HIAA to be lower in depressed patients than in controls (5–9). Most but not all studies have also reported lower levels of CSF 5HIAA in manic patients than in normal controls (5, 10–15). Acute treatment of manic and depressed patients with lithium has been reported to increase levels of 5HIAA in cerebrospinal fluid (16). However, in another study of urinary turnover of 5HIAA, acute lithium therapy in depression reduced levels of 5HIAA (17). Normals treated for one week with lithium carbonate evidenced no change in 5HIAA urinary output (18). In contrast, long-term lithium treatment in euthymic bipolar patients has been found to increase CSF concentrations of 5HIAA (19). One can only conclude that lithium may decrease urinary 5HT turnover while increasing levels of 5HIAA in cerebrospinal fluid (Table 1).

Platelet uptake is thought to be a model of presynaptic nerve uptake; platelet content may be a model of presynaptic nerve content (21). Platelet studies of serotonin function have focused on serotonin uptake and content. Most (20–27) but not all (28) studies have reported reduced serotonin uptake in platelets taken from depressed patients. These results also show a lower serotonin uptake in platelets from depressed patients with a history of mania or hypomania than in platelets from depressed patients without such a history (20–22). Manic patients have also been shown to have lower platelet serotonin uptake than controls (21). Although acute lithium treatment of manic patients has been found to reduce platelet serotonin uptake sites (29), long-term lithium prophylaxis has been found to increase platelet serotonin uptake toward normal (25, 29–30). As might then be expected, a three-week period of lithium discontinuation led to a significant reduction in platelet serotonin uptake (31). Furthermore, platelet serotonin content has been found to be higher in depressed patients with history of mania or hypomania than in controls (20). Acute lithium treatment of depressed patients (33) as well as long-term prophylaxis has been found to decrease platelet serotonin content. Three weeks of lithium discontinuation in euthymic bipolar patients led to an increase in platelet serotonin content similar to that seen in depressed patients with history of mania or hypomania (31). Recently, prophylactic lithium treatment was found to lead to an increased serotonin-induced platelet aggregatory response in bipolar and unipolar patients (34) (Table 2).

Finally, neuroendocrine studies (Table 3) have focused on agents that influence presynaptic serotonin mechanisms (tryptophan and 5-hydroxytryptophan, 5HTP), and that influence serotonin release (fenfluramine). Abnormal increases in serum prolactin following intravenous tryptophan have been reported in depressed patients (35). Abnormal increases in serum cortisol after oral 5-hydroxytryptophan have been reported both in depressed and in manic patients

TABLE 2

Platelet Serotonin Effects of Lithium Carbonate

Author & year (ref)	Parameter	Population (no.)	Base-line	Treat-ment	Prophy-laxis	With-drawal
Meltzer 1981 (21)	Uptake (picomole/10^7 plts/min)	Controls (20)	11.1	—	—	—
		Manic (14)	9.7	—	—	—
		Depressed				
		Bipolar (11)	5.7	—	—	—
		Unipolar (11)	8.1	—	—	—
Raisman 1982 (26)	Uptake V_{max} (pmol/10^8 plt/4 min)	Controls (27)	15.7	—	—	—
		Depressed (14)	9.6	—	—	—
Rausch 1982 (27)	Uptake (nmole/10^{11} plt)	Controls (7)	2.57	—	—	—
		Depressed (7)	1.81	—	—	—
Stahl 1983 (20)	Content (ng/10^8 plt)	Controls (66)	69.7	—	—	—
		Depressed				
		Bipolar (11)	103.7	—	—	—
		Unipolar (14)	84.5	—	—	—
	Uptake (pmole/10^8 plt)	Controls (25)	29.9	—	—	—
		Depressed				
		Bipolar (11)	18.9	—	—	—
		Unipolar (14)	34.4	—	—	—
Born 1980 (25)	Uptake (nmole/10^{10} plts 5 min)	Controls (10)	29.81	—	—	—
		Euthymic (8) bipolar + unipolar unmedicated	20.88	—	—	—
		Euthymic (10) bipolar + unipolar	—	—	27.88	—
Coppen 1980 (30)	Uptake V_{max} (pmole/10^8 plts/min)	Controls (32)	30.6	—	—	—
		Depressed (26)	23.2	—	—	—
		Recovered depressed (25)	19.5	—	—	—
		Euthymic unipolar (28)	—	—	27.8	—
		Euthymic bipolar (7)	—	—	33.0	—
		Recovered depressed (8)	14.1	—	28.6	—
Meltzer 1983 (29)	Uptake V_{max} (pmole/min/10^7 plts)	Manic (14)	9.52	7.44	—	—
		Depressed hx mania (7)	9.04	8.34	—	—
		Manic + depressed (7)	—	9.30	17.45	—
Wirz-Justice 1978 (32)	Content (nmole/mg platelet protein)	Controls (43)	1.94	—	—	—
		Bipolar depressed	2.67 (unchanged after switch to hypomania)			
Corona 1982 (33)	Content (ng/ml plasma)	Depressed (37)	4.32	3.56	—	—
Goodnick 1984 (31)	Content (ng/10^8 plts)	Euthymic bipolars (10)	—	—	67.0	102.0
	Uptake V_{max} (pmole/10^7 plts/min)	Euthymic bipolars (10)	—	—	14.8	11.3

(36). The abnormal increase in serum cortisol after 5-hydroxytryptophan appears to persist in unmedicated euthymic bipolar patients (37). Acute lithium treatment in manic patients increases the serum cortisol response to 5-hydroxytryptophan (38). However, during long-term lithium prophylaxis, similar to results governing response of platelet serotonin uptake and content, the serum cortisol response to 5-hydroxytryptophan reverses to bring the response closer to that in normal controls (39). Thus, after three weeks of lithium discontinuation, the serum cortisol response to 5-hydroxytryptophan again increases to that in depressed and manic patients (37). A mixed group of unipolar and bipolar patients with major depressive disorder have been found to have abnormal prolactin responses to oral fenfluramine (40). Another study found that in contrast to both controls and unmedicated euthymic bipolar patients, lithium-treated euthymic bipolar patients had increases in plasma cortisol concentrations after fenfluramine (41).

Clinical Implications. There are several clinical implications of the human psychopharmacology studies of lithium influences on serotonin in manic-depressive disorder. First, whenever lithium application is either limited or contraindicated, other serotonin-based treatments may be of value in both acute therapy and in prophylaxis. Some patients may not be able to tolerate lithium's side effects (tremor, diarrhea, nausea) and never attain a minimally effective plasma level of lithium for either acute therapy or prophylaxis. For other patients, lithium may be rela-

TABLE 3
Neuroendocrine Effects of Lithium Carbonate

Author & year (ref)	Parameter	Population (no.)	Baseline	Treatment	Prophylaxis	Withdrawal
Meltzer 1984 (36)	Peak-baseline serum cortisol (μg/dL) to 5HTP 200 mg	Controls (15)	3.0	—	—	—
		Depressed (31)	7.9	—	—	—
		Manic (16)	9.0	—	—	—
Meltzer 1984 (38)	Peak-baseline serum cortisol (μg/dL) to 5HTP 200 mg	Manic (7)	10.0	13.4	—	—
Goodnick 1985 (39)	Peak-baseline serum cortisol (μg/dL) to 5HTP 200 mg	Manic (3)	11.0	14.0	4.5	—
Goodnick 1986 (37)	Peak-baseline serum cortisol (μg/dL) to 5HTP 200 mg	Controls (5)	5.2	—	—	—
		Euthymic bipolars (3)	—	—	10.8	15.2
Muhlbauer 1985 (41)	$(T_{+4\,hr}-T_{+2\,hr})$ Plasma cortisol to fenfluramine 60 mg (nmol/L)	Euthymic bipolars unmedicated (8)	−6.1	—	—	—
		Euthymic bipolars on lithium (11)	—	—	114.8	—

tively or completely contraindicated because the patient is in the early stages of pregnancy or has had myocardial infarction, renal disease, temporal lobe epilepsy, myasthenia gravis, or myeloid leukemia (42). In these situations, it is heartening that serotonin precursors have been used effectively to treat depression and mania, as well as provide prophylaxis. A recent review of six double-blind and seven open studies of 5-hydroxytryptophan concluded that this medication has definite antidepressant properties (43). L-tryptophan has been found to be effective in five of ten double-blind studies in depressed patients (43). L-tryptophan has also been found to be effective in the treatment of mania (44–46). Finally, there is further evidence of prophylactic effect of l-tryptophan in preventing recurrences of mania and depression. (For detail on results and dosages, see Table 4.)

Finally, in the situation where lithium at acceptable plasma levels either with or without adjunctive tryptophan has not been effective in the treatment or prevention of manic-depression, one may conclude that the patient's brain disorder is not in serotonin, but rather in norepinephrine since lithium has relatively little effect on norepinephrine (37, 48). For these patients, carbamazepine would be indicated for both treatment and prophylaxis. Carbamazepine in a number of studies has been shown to effectively treat and prevent manic-depressive disorder (49). Carbamazepine has been shown to have significant effects on brain norepinephrine but to have relatively little effect on serotonin (50). Perhaps for this reason, carbamazepine has been used successfully together with lithium in manic-depression to produce complete remission not previously possible on lithium alone (51); carbamazepine may stabilize norepinephrine at the same time that lithium is stabilizing serotonin.

In conclusion, abnormalities reported in serotonin metabolism, platelet serotonin indices,

TABLE 4
Serotonin Precursors in Treatment of Manic-Depressive Disorder

Author & year (ref)	Medication	Dosage	Population (no.)	Response
Van Praag 1981 (43)	5-Hydroxytryptophan	200–300 mg/day	Major depressive	Summary of 6 studies: 46/71 improved
Brewerton 1983 (45)	L-tryptophan	9 gm/day	Mania (9) Schizoaffective mania (7)	Significantly better than placebo
Chouinard 1985 (46)	L-tryptophan	12 gm/day	Mania (24)	After 1 week, significant improvement in CGI mania score
Beitman 1982 (47)	L-tryptophan	2 gm/day	Bipolar 2 (1)	On A-B-A design, patient clearly less vulnerable to manic and depressive relapse

and serotonin-based neuroendocrine challenge tests in depressed, manic, and euthymic bipolar patients are influenced by lithium treatment. When lithium is used acutely to control symptoms of mania and depression, lithium tends to further exaggerate the abnormality found in platelet serotonin uptake as well as in the serum cortisol response to 5-hydroxytryptophan. This may be the fastest way to reestablish normal serotonin status in synapses, i.e., to decrease presynaptic uptake and increase postsynaptic sensitivity. However, when lithium is used for long-term prophylaxis, lithium induces a reversal of platelet serotonin uptake and neuroendocrine responses toward control levels. The clinical implications are that when lithium cannot be used for treatment, serotonergic precursors may be effective in the therapy of manic-depressive disorder, and when lithium has been used appropriately for sufficient time without response, another noradrenergic but nonserotonergic agent, carbamazepine, should be used either with or without lithium.

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Pulmonary Medicine Notes

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This is the first in a series of Notes dedicated to pulmonary medicine for the Mount Sinai Journal. *Over the past two decades, the field of pulmonary medicine has vastly expanded, and it now shares common interests with other medical subspecialties, such as critical care, neurology, cardiology, and oncology. The Notes section will reflect this by presenting original clinical and experimental work as well as case reports and reviews covering all aspects of chest diseases and therapeutics.—BPK*

Diaphragmatic Flutter in a Patient With Lymphoma

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Abstract

Diaphragmatic flutter has been associated with many different conditions. Approximately sixty cases have been reported in the literature, the majority being diagnosed on clinical, fluoroscopic, spirometric, and electromyographic data. We describe flutter of the diaphragm associated with lymphomatous infiltration of the leptomeninges in a patient who was unable to be weaned from mechanical ventilatory support. Respiratory inductive plethysmograph was used to diagnose, follow, and evaluate the response of several therapeutic maneuvers. This is the first description of diaphragmatic flutter associated with lymphoma or being a cause of failure to wean from a ventilator.

Diaphragmatic flutter is a relatively benign and rare disorder (1). In 1723, Antony Van LeeuWenhoek, "father of microscopy," complained of epigastric pulsations and shortness of breath (2). He was diagnosed by his personal physician as having "palpitations of the heart," but, after counting his pulse, LeeuWenhoek concluded that the epigastric beats had their origin in the diaphragm. This represents the first recorded case of a disorder that has been referred to as "diaphragmatic flutter," a most unusual disturbance of diaphragmatic motility.

In this report we describe diaphragmatic flutter in a critically ill patient who was followed up with respiratory inductive plethysmography.

Case Report. A 60-year-old white man was admitted with a one-day history of increasing agitation, disorientation, confusion, and difficulty walking. Pertinent past history included insulin-dependent diabetes mellitus for 10 years. His temperature was 101°F, pulse 144/min, respiratory rate 46/min, and blood pressure 140/80 mmHg. There was no nuchal rigidity. Chest examination showed normal configuration; bibasalar inspiratory crackles were auscultated. A peculiar rhythmic motion of the upper abdomen in the epigastric area was seen. Palpation suggested asynchrony between the rib cage and abdomen. Neurologically the patient was confused, disoriented, and lethargic. He withdrew to painful stimuli but did not follow simple commands. Deep tendon reflexes were diminished throughout and muscle strength appeared symmetrical but reduced.

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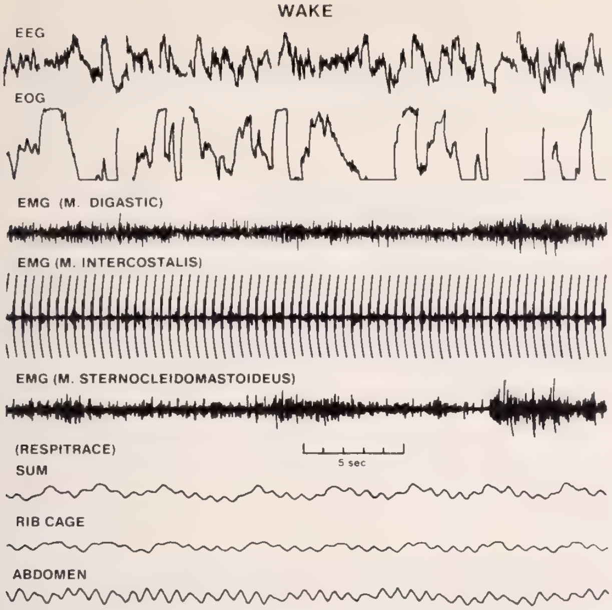

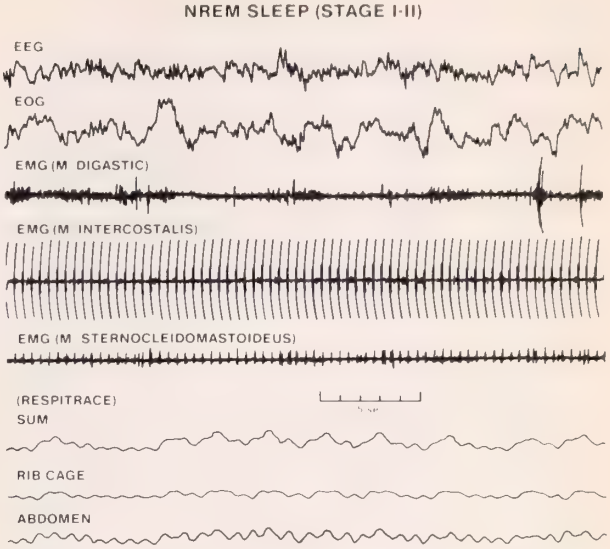

Fig. 1. Left Electroencephalographic (EEG), electroculographic (EOG), electromyelographic (EMG), and respiratory inductive plethysmographic tracings during a wakeful state during which patient attempted to alter his breathing pattern. Rhythmic spikes seen in intercostal EMG were electrocardiograph (EKG) interference; chaotic EMG activity represented the patient's conscious efforts to modify his breathing frequency. Diaphragmatic flutter waves were reflected in abdomen signal; rate, 78/min. **Fig. 2. Right** During non-REM (NREM) sleep stage I-II, diaphragmatic flutter rate was 72/min. Except for EKG interference, there was no EMG activity in intercostal or sternocleidomastoid muscles. Rib cage tracing is opposite in direction to abdomen and sum signals, which is indicative of rib cage paradox. Also seen was a slower rate superimposed on flutter rate (dirhythmic breathing).

Laboratory findings included leukocyte count of 4,500/mm^3, with 11% neutrophils, 27% band forms, 40% lymphocytes, 18% monocytes, and 4% atypical lymphocytes. The blood glucose was 351 mg/dl and serum calcium was 14.1 mg/dl. CT scan of the brain showed no evidence of mass effect. Spinal fluid analysis revealed 150 red blood cells, 51 white blood cells (83% atypical lymphocytes and 17% histiocytes); protein, 57 mg/dl; glucose, 136 mg/dl (peripheral blood glucose, 183 mg/dl at time of procedure). Spinal fluid gram, india ink, cryptococcal antigen, acid-fast bacilli, and fungal smears were all negative. An electroencephalogram was consistent with metabolic encephalopathy. Bone-marrow aspirate and biopsy was consistent with malignant lymphoma, pleomorphic type; the cells were morphologically identical to the atypical lymphocytes seen in the spinal fluid.

Endotracheal intubation with mechanical ventilation was required because of tonic-clonic seizures and respiratory distress. Aggressive therapy for the patient's hypercalcemia (hydration, corticosteroids, diuretics, and calcitonin) reduced the serum calcium to 9.3 mg/dl. The patient was treated with intrathecal methotrexate for meningeal involvement by malignant lymphoma. After receiving several courses of intrathecal methotrexate, the patient's mental status improved and the seizures were controlled.

During mechanical ventilation, the rhythmic motions in the patient's epigastric area persisted and all attempts at weaning failed. A breathing pattern analysis was obtained using respiratory inductive plethysmography (Respigraph, NIMS, Inc., Miami Beach, FL), which revealed an irregular rhythmic fluttering of the diaphragm at a rate of 50–78/min; each flutter volume was 300–500 ml. The patient could not voluntarily alter these movements, despite having a clear sensorium (Fig. 1). In addition, the diaphragmatic flutter waves could not be suppressed by mechanical hyperventilation and there were no associated hiccups. Simultaneous electromyographic recordings of the digastric, intercostal, and sternocleidomastoid muscles during sleep showed no evidence of flutter in these muscle groups (Fig. 2). Several therapeutic maneuvers were attempted to suppress the diaphragmatic contractures, including diphenylhydantoin (with therapeutic levels), intravenous diazepam, intravenous chlorpromazine, and oral valproic acid. The flutter was unaffected by any of these medications. Continued attempts to wean the patient from the ventilator failed, and the diaphragmatic flutter persisted. Eventually, the patient succumbed to gram-negative septicemia.

Discussion. Diaphragmatic flutter has been variously designated "palpitations of the diaphragm," "convulsions of the diaphragm," "diaphragmatic cramps," "rhythmic spasms of the diaphragm," "diaphragmatic rumble," "flutter-fibrillation of the diaphragm," and "diaphragmatic myoclonus." The term "diaphragmatic flutter" was coined by Porter in 1936 (3) in his description of an unusual clonic disturbance of diaphragmatic motility that simulated angina pectoris and was characterized by irregular paroxysmal contractions superimposed on normal diaphragmatic activity. Flutter of the diaphragm may occur in concert with myoclonus of the other respiratory muscles (respiratory myoclonus) or alone.

In the majority of cases previously reported, the initial diagnosis was a psychogenic or hysterical disorder of breathing (4). Common complaints include respiratory distress, muscular fatigue in the abdominal wall (especially in the epigastrium), and pain in the lower costal borders (1). Paroxysmal or irregular beats of the abdominal wall unrelated to the heart beat, associated with tachypnea and peculiar sounds during auscultation of the precordium, epigastrium, or lower costal border are common physical findings (1).

Most cases of diaphragmatic flutter have no clear-cut etiology (1). The most common central nervous system association is epidemic encephalitis, but tumors, multiple sclerosis, and vascular insufficiency to the brain stem area have been recorded (4). Peripheral or local processes may also be associated with diaphragmatic flutter. Cervical ribs, rheumatic heart disease, mediastinal lymph nodes, pleurisy, peritoneal adhesions, and fracture of the xiphoid process have also been described (5).

Diaphragmatic flutter is usually diagnosed on the basis of clinical, fluoroscopic, spirometric, and electromyographic findings. In our patient, diaphragmatic flutter was associated with lymphomatous infiltration of the leptomeninges. Respiratory inductive plethysmography allowed us, by noninvasive means, to confirm the diagnosis and follow the disorder in a critically ill patient in the intensive care unit. We were also able to evaluate his response to several therapeutic maneuvers by continuous monitoring.

Several important points were highlighted in this case. First, the flutter of the diaphragm was probably peripheral, because there was no evidence of irregular contraction (as seen in the electromyograms) of the digastric, intercostal, or sternocleidomastoid muscles. Second, we were unable to suppress or abolish the flutter with therapeutic doses of agents reported to be helpful in isolated circumstances (1, 4, 6). Third, we were able to noninvasively follow the abnormal breathing pattern of a critically ill patient. Last, the diaphragmatic flutter contributed directly to the patient's inability to wean from mechanical ventilation.

In conclusion, diaphragmatic flutter is a rare disorder that has been associated with many different medical conditions. Because of the frequently bizarre symptomatology, diagnosis may be delayed, and referral for psychiatric assessment is common (7). By using respiratory inductive plethysmography, one is able to diagnose and follow this disorder noninvasively, even in critically ill patients.

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Reproductive Medicine Notes *Norbert Gleicher, M.D., editor*

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Hospital Guidelines for Fetal Viability Assessment and Postdecision Responsibilities

STEPHEN A. MYERS, D.O.

Improved survival of very low birth weight (VLBW) infants is commonplace. A 1000-gram infant that would have been perceived to be previable 10 or 15 years ago currently enjoys a bright prognosis. Many centers have reported optimistic neonatal survivals (1–4), including assessments of long-term outcomes (3, 4). As the overall prognosis for the VLBW infant has improved, the gestational age and birthweight at which the fetus is considered viable has become lower and lower. This phenomenon has been accompanied by legitimate concerns about the cost of this improved survival in medical (5–9), ethical (10), and economic (11) terms. As these difficult issues continue to evolve, no one can be certain what the final answers to any of these questions may be. Indeed, if the past can teach us anything, we must recognize the fact that the answer to these questions may continue to change with time.

It is not my purpose here to add any additional information to the voluminous literature on short-term and long-term survival of VLBW infants. What is my purpose, however, is to focus attention on two points usually ignored in articles on this topic: the actual line-drawing process, and postassessment ("postdecision") responsibilities.

Titles such as "Where to draw the line?" (2) and "How small is too small?" (12) carry an inherent implication that there is clearly a group of neonates who have no reasonable chance for survival, a group often referred to as "previable." The data in such discussions support such an implication. However, problems may arise if all other neonates are assumed to be in only one other mutually exclusive category, viable. For example, although both a 23-week, 600-gm neonate and a 30-week, 1400-gm neonate are (in practice and theory) viable, they have very different probabilities for any given outcome.

Avoiding Either/Or: Three Categories. The inherent problem that occurs when only two mutually exclusive groupings are considered can be obviated if an intermediate category is created (Table). The effect of creating three mutually exclusive groups can ease some of the difficult postdecision responsibilities that must take place. The choice of viability assessments then is between "previable" (<10% survive), "viable" (>50% survive), and "intermediate or borderline" (20%–40% survive). Although different institutions, locations, or areas may dictate a change in the actual birthweight or gestational age that defines the three classes, one of the three mutually exclusive determinations can always be made.

By taking this approach, a reasonable set of actions can be predicted to follow, termed here the postdecision actions. These include chart documentation of obstetric data, individual survival statistics, the parents' acknowledgement of this information, the patient's wishes for operative intervention for fetal indication, the use of continuous electronic fetal monitoring, the use of nonsurgical treatment for fetal distress, and the resuscitation required.

Viable. At our institution, based on this thinking and our own in-house capabilities and experience, any fetus estimated to be above 700 grams in weight, or at least 24 weeks gestational age, is considered viable. The patient-specific data are

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TABLE

Hospital Guidelines for Fetal Viability Assessment and Postdecision Responsibilities Before, During, and After Delivery

Best obstetric estimate of gestational age	Less than 22 wks (under 500 gms)		$22\frac{1}{7}$ to $23\frac{6}{7}$ wks (500–700 gms)		24 wks and over (over 700 gms)	
Viability assessment	Previable (<10% survival)		Intermediate viability (borderline 20%–40% survive)		Viable (>50% survival)	
Chart documentation of all data with specific numbers	Yes		Yes		Yes	
Patient's acknowledgment of receiving above information	Yes		Yes		Yes	
If patient declines operative intervention for fetal distress	Declining is appropriate		Declining may be appropriate		Consider contacting clergy, hospital administration, family, legal	
Fetal monitoring	Unnecessary		Optional		Necessary	
Nonsurgical Rx for fetal distress	Unnecessary		Recommended		Necessary	
Result	Stillborn	Liveborn	Liveborn	Stillborn	Stillborn	Liveborn
Resuscitation	N/A	Pediatric staff in attendance/appropriate resuscitation		N/A		Pediatric staff in attendance

recorded in the chart with an acknowledgement that the patient understands the expected prognosis. Rarely, a patient may decide to decline operative intervention for fetal indication. Should this occur, contacting appropriate family members and administrative, clergy, and legal personnel is usually successful in resolving the problem. Maternal versus fetal rights have been discussed in detail elsewhere (10, 13), but all institutions would do well to take Bowes' suggestion; he recommends that an institutional policy be formulated before such an event occurs, to equip the staff in handling such an occurrence (12). The remaining issues related to monitoring, the treatment for fetal distress, and resuscitation require no further discussion.

Previable. Conversely, any fetus estimated to be under 500 grams birthweight or under 22 weeks gestational age is considered to be previable. Similar chart documentation of both the obstetric information and the patient acknowledgement is necessary. Operative intervention for fetal indication for this group would be ridiculous, and having a patient decline such intervention must be considered entirely appropriate. (I have not had the personal experience of having a patient request operative delivery under these circumstances, although I suspect sooner or later this will occur. Prospective departmental recommendations, as Bowes suggests, may make this situation more tolerable). Fetal monitoring and other nonsurgical intervention for the fetus is unnecessary in this group, and in fact may only help lower the patient's emotional status or falsely raise her expectation. What is important is that all delivery room staff be prepared for the possibility of the delivery of a liveborn viable fetus. When this occurs, appropriate pediatric intervention *must* be made, independent of prior obstetric decisions. Most neonatal services have reasonable guidelines for the management of such cases, and fortunately, prolonged, expensive intervention for the 400-gram liveborn is rare. Not rare, however, is the 700- or 800-gram liveborn who was thought to be previable and was not ideally resuscitated. It cannot be overstated that proper moral and medicolegal considerations dictate proper pediatric attendance for all liveborn infants.

Borderline Viability. The remaining group of infants, those with predicted birthweights between 500 and 700 grams, or with a gestational age between $22\text{-}\frac{1}{7}$ weeks and $23\text{-}\frac{6}{7}$ weeks, are considered to be of intermediate viability. For this group, individual medical, social, religious, and economic factors may potentially tip the scales of the decision-making process in one direction or another. For a young multipara, the desire for a particular course may be very different than for the 40-year-old infertility patient, given that delivery is imminent. The balance that must be sought between fetal and maternal rights is not absolute and must be individualized. Even uneducated patients can be brought into the decision-making process. When a proper explanation is made in terms the patient can understand, it is not difficult to determine whether an individual patient wants you to "do everything possible." Moreover, even for the patient who declines operative intervention for fetal indication, fetal monitoring and nonsurgical intervention for fetal distress can be beneficial. Kitchen has demonstrated that 85% of these fetuses can tolerate labor without fetal distress (3). These patients can clearly benefit from the reassurance that normal fetal heart rate monitoring can give. For the remaining patients, fetal monitoring can indicate that other measures are necessary—oxygen, repositioning, tocolytics, possibly amnio infusion. Moreover, if fetal distress develops and nonsurgical intervention is not effective, the patient may change her mind. The patient and her fetus deserve that opportunity. Issues about resuscitative efforts have already been addressed.

These recommendations have been discussed within our institution. They have been distributed to the medical and nursing staff to use as a framework in the management of patients who will deliver a VLBW infant. Having these departmental recommendations has already made the postdecision process easier for some patients and staff. Although other institutions may choose to alter these recommendations based on their own capabilities or the desires of their staff, having some recommendations can make the process easier. Whatever the individual guidelines concerning the postdecision process may be, if categorization is kept to the three groups—previable, borderline viability, and viable—difficulties may be avoided.

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Letters

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Multiplicity of Causes for Adrenal Damage in AIDS

To the editor: We here describe recent autopsy observations of adrenal pathology in two cases of the acquired immunodeficiency syndrome (AIDS), and discuss the role of cytomegalovirus (CMV) and other factors therein. Further, we add to the known cases of the ultimate inadequacy of current antiviral agents in the therapy of CMV infection in this patient population.

Case 1. A 30-year-old homosexual man receiving suramin for AIDS developed adrenocortical insufficiency and required dexamethasone and fludrocortisone. Corticosteroid dosages were augmented during stresses, e.g. bouts of *Pneumocystis* pneumonia. Despite vigorous home therapy with electrolyte solutions, symptomatic dehydration with salt wasting, ascribed to hypoadrenalism, required repeated hospitalization.

The patient died of gastrointestinal bleeding. Autopsy showed disseminated CMV infection with extensive bowel involvement, and lesser mycobacteriosis. Multiple histologic sections of the atrophic adrenals showed, in addition to atrophy, abundant fresh and old necrosis, with CMV inclusions in most of the sparse recognizable adrenal cells. No adrenal co-infection with other organisms was demonstrable. Intact adrenal cells were estimated at 1% of normal.

Case 2. A 31-year-old homosexual man with AIDS had been treated for one year with the experimental drug DHPG, for CMV retinitis. Eventually retinitis progressed, his condition deteriorated, and progressive respiratory failure led to death. There was never adrenal insufficiency. Autopsy showed polymicrobial pneumonitis, with a prominent CMV component; disseminated CMV infection; and scant CMV adrenalitis. No co-infection of the adrenal was demonstrable.

What caused the adrenal damage in these cases, particularly case 1? First, although chronic corticosteroid treatment produces adrenal atrophy, it does not cause necrosis. Second, CMV adrenalitis and adrenal necrosis have been well described in AIDS patients with disseminated CMV infection, with a spectrum ranging from the minimal involvement seen in case 2, to pure medullary disease (1), to whole-organ necrosis (2). CMV adrenal tropism appears relatively specific to AIDS, since adrenal involvement has not been reported to our knowledge in other immunoincompetent populations. Studies of CMV infection in athymic nude mice show that virulence in the adrenal parallels defective T-cell function (3). The absence of T-lymphocyte function in these mice produces a deficit in cell-mediated immunity similar to that in AIDS patients, so that they appear to constitute a valid model.

Third, the role of suramin toxicity in adrenal insufficiency remains unclear. Suramin used for pemphigus was reported to cause fatal adrenocortical degeneration in 1937 (4). Subsequent studies provided conflicting evidence, including similar adrenal histopathology in untreated pemphigus (5). No adrenal insufficiency has been documented in suramin-treated African trypanosomiasis and onchocerciasis (5). Thus, recent associations of suramin and adrenal insufficiency in AIDS patients (4) may underestimate the multifactorial damage we have observed. For example, in case 1, firm conclusions are impossible concerning the relative adrenal insults produced by CMV infection; by chronic corticosteroid therapy; by suramin therapy; and by possible human immunodeficiency virus (HIV) infection of adrenal tissue (1).

Future studies to clarify these contributing causes might concentrate on autopsy study of adrenals that were functionally insufficient, in AIDS cases that prove histologically free of adrenal CMV infection, if any such cases can be found; as well as on a search for HIV itself in such adrenals.

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A Clinical Fragment in Immunology

To the editor: The discussions by you [Constantin Bona, guest editor, issue "Immune Genes"] and others in the March 1986 *Mount Sinai Journal* are quite beyond my comprehension. I am an old psychiatrist, ignorant of the branch of biology which these researches relate to.

But for what it is worth, it occurred to me to write you a clinical detail which might interest you. I am nearly 93 years old, and in fairly good health. Although repeatedly exposed, I have never had measles, scarlet fever or mumps. When I was about 12 or 14, my two younger brothers were very *severely* ill with scarlet fever. I lived in the house (not in their sick room).

When I was in medical school, I volunteered for service on the infectious disease wards (children's hospital) and later took care of people with measles, typhoid fever, scarlet fever and 0-5 meningitis. It was noted at the time by my teachers and colleagues that I seemed to have a peculiar immunity from such infections. They were all afraid of "catching" something. I don't recall if they did.

I occasionally get coryza and bronchitis like other people, whether or not I take flu vaccine shots. I did not have the flu during the epidemic of 1918–19; I was professionally in charge of sick hospital personnel during that alarming period. We lost several nurses. (My wife, who lived with me in the hospital, was severely ill.)

It occurred to me that this fragment of clinical history might have some meaning to your colleagues in immune and symptomatology studies.

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Mayer B. Davidson and Glenn D. Braunstein
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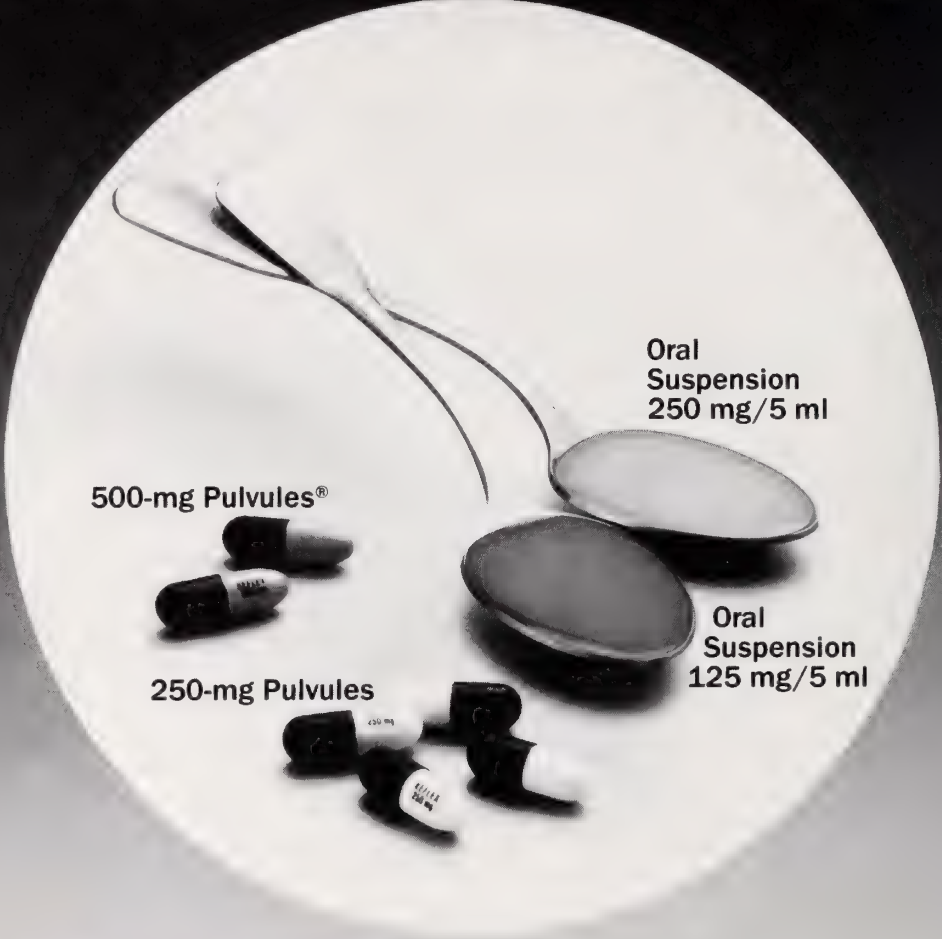
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Introduction

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Diabetes Mellitus: Recent Developments In Treatment

Cedars-Sinai Medical Center has had a long and important association with the syndrome of diabetes mellitus. In 1920, Dr. Moses Barron, who subsequently became a consultant in internal medicine at Cedars of Lebanon Hospital (which later merged with Mount Sinai Hospital in 1976 to become the present-day Cedars-Sinai Medical Center) published a paper (1) describing patients with pancreatic lithiasis in whom complete atrophy of the acinar tissue developed, leaving the islets of Langerhans intact. As all students of diabetes know, insulin was first successfully extracted from dogs by ligating the pancreatic ducts, allowing destruction of the exocrine tissue, after which the remaining endocrine tissue was treated. The idea for using this approach came to Dr. Banting as a direct result of reading Dr. Barron's paper, as he wrote in a letter to Dr. Barron (Fig.).

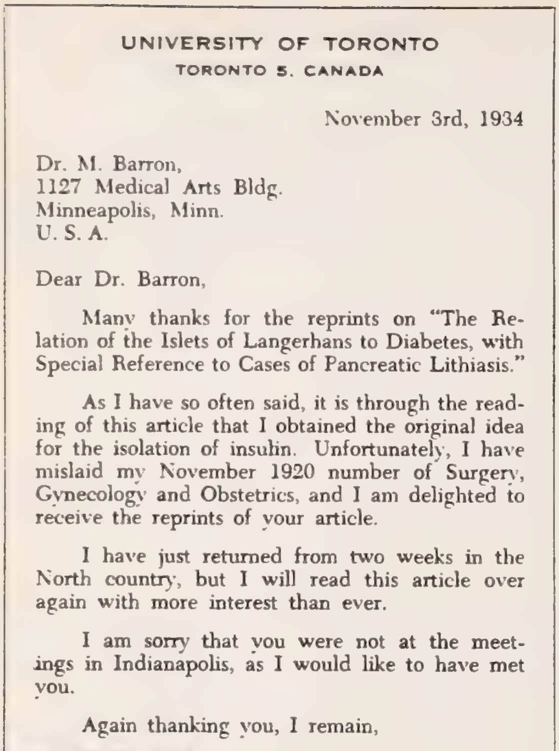
The current well-accepted notion that sulfonylurea agents have important extrapancreatic effects was first demonstrated 30 years ago by Dr. Raymond Caren and Lucille Corbo (2) working in the Institute for Medical Research at Cedars of Lebanon Hospital. (Lucille Corbo is still working in diabetes research at Cedars-Sinai in the laboratories of Dr. Naomi Neufeld, a participant in this issue.) This seminal observation lay fallow for over 20 years until the data on sulfonylurea-agent-stimulated insulin secretion forced investigators to reconsider an extrapancreatic effect for these drugs.

The third major contribution to diabetes emanating from the Mount Sinai Hospitals occurred when Dr. Arnold Kadish, also working in the Institute for Medical Research, developed the first instrument for the continuous measurement of blood sugar (3). This breakthrough was the forerunner of the artificial endocrine pancreas (Biostator), which is currently not only providing valuable research data, but is also used in the treatment of hyperglycemia in diabetic patients in unstable situations.

Cedars-Sinai Medical Center has continued this tradition of involvement in diabetes. In 1979, the Alfred Jay Firestein Diabetes Program was established through the generosity of the Factor and Firestein families in memory of one of their members, who unfortunately died from the complications of type 1 diabetes mellitus at the young age of 46 years. The program is also supported by the proceeds of the Monty Hall Five Tennis Tournament and the Diabetes Unit of Group Effort, the latter founded by Mrs. Lynn Klinenberg, the mother of a type 1 diabetic patient.

The Alfred Jay Firestein Diabetes Program encompasses patient care, education, and research. It is housed in 2000 square feet of laboratory space in which three physicians, two Ph.D.'s, one M.D. research fellow, and three research technicians carry out basic research in the cause and treatment of diabetes. Clinical studies, some utilizing a Biostator, are performed elsewhere in the medical center. The inpatient unit consists of 32 beds specifically allocated for diabetic patients with nurses specially trained to handle diabetic problems. Two to three house staff members and medical students rotate through the ward every month. In addition to education on the Diabetes Ward, patients are taught one-to-one as outpatients by a nurse educator. Moreover, a five-day Diabetes Outpatient and Training Center was recently established to enable patients to manage their own diabetes under the guidance of their physicians (discussed in Michael Bush's paper in this symposium). Finally, the Alfred Jay Firestein Diabetes Program also includes the opportunity for selected patients to be treated with insulin pumps (described in Carol Rosenberg's article in this issue). The personnel to carry out all of this house staff and patient teaching include three diabetologists, two diabetes nurse educators, a dietitian specifically trained in diabetes, and a nurse to handle the Biostator and insulin pump patients.

Summarizing Knowledge to Change Outcomes. Although this symposium recognizes Cedars-Sinai's commitment to diabetes through the Alfred Jay Firestein Diabetes Program, its primary function is to summarize the current state of knowledge in many areas of diabetes for the readers of this journal, most of whom are internists. Currently, over 80% of diabetic patients are cared for by primary care physicians. Our track record needs improvement. At the present time, diabetes (with its vascular complications) is



UNIVERSITY OF TORONTO
TORONTO 5, CANADA

November 3rd, 1934

Dr. M. Barron,
1127 Medical Arts Bldg.
Minneapolis, Minn.
U. S. A.

Dear Dr. Barron,

Many thanks for the reprints on "The Relation of the Islets of Langerhans to Diabetes, with Special Reference to Cases of Pancreatic Lithiasis."

As I have so often said, it is through the reading of this article that I obtained the original idea for the isolation of insulin. Unfortunately, I have mislaid my November 1920 number of Surgery, Gynecology and Obstetrics, and I am delighted to receive the reprints of your article.

I have just returned from two weeks in the North country, but I will read this article over again with more interest than ever.

I am sorry that you were not at the meetings in Indianapolis, as I would like to have met you.

Again thanking you, I remain,

Yours sincerely,

F. G. Banting, M.D.

A copy of Dr. Banting's letter thanking Dr. Barron (left) for his critical contribution to the life-saving discovery of insulin. *From The Journal-Lancet 1959; 79:521–522.*

the third leading cause of death in the United States; diabetic patients are 25 times more likely to become blind, 17 times more likely to develop renal disease, 20 times more likely to develop gangrene, and twice as likely to suffer a heart attack or stroke than their nondiabetic counterparts.

Thus, diabetes is the leading cause of new cases of blindness in this country, underlies the renal failure of 25% of all patients on dialysis (projected to be 50% in 10 to 15 years), is behind nearly 80% of all of major amputations, and accounts for approximately $14 billion a year in medical care cost—not including lost wages and productivity. The suffering is incalculable.

Much of this dreadful toll need not happen. Strict control of diabetes (4) and appropriate preventive measures can reduce this morbidity and mortality drastically. However, the dismal statistics will not change until the knowledge and clinical approaches summarized in this symposium are incorporated into the practice of the physicians caring for diabetic patients.

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The endowment of the Alfred Jay Firestein Diabetes Center at Cedars-Sinai is an outreach of love in memory of one diabetes patient to all those whose lives are touched by the physical and mental trauma of this ailment. We are deeply appreciative for the dedication of the Center's medical staff in establishing its superb program and under whose direction the Center's goals of patient care, education and research are being realized. For today, the care of those in need is essential. It is our deepest, most heartfelt wish that from these roots we shall harvest both prevention and a cure.—*The Family of Alfred Jay Firestein*

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The "Secret" of the Islets: A Footnote to History

The role of Moses Barron in the discovery of insulin has almost an apocryphal ring. Late one night in October 1920, Frederick Banting took a copy of *Surgery, Gynecology and Obstetrics* to bed to read himself to sleep. He had already begun his studies on carbohydrate metabolism, so the article that caught his eye was one entitled "The Relation of the Islets of Langerhans to Diabetes with Special Reference to Cases of Pancreatic Lithiasis." The article was written by a pathologist at the University of Minnesota, a Dr. Moses Barron, who had observed, in autopsy studies of patients with pancreatic lithiasis, that early in the disease the islets were preserved, hence diabetes did not occur; conversely, late in the disease, degenerative changes in the islets resulted in hyperglycemia and glycosuria. On the basis of these observations he concluded that "the islets secrete a hormone directly into the lymph or blood streams (internal secretion), which has a controlling power over carbohydrate metabolism." After reading this article, Banting recalled that he was unable to sleep and at 2 AM jotted down in his notebook:

> Ligate pancreatic ducts of dog. Keep dogs alive till acini degenerate leaving Islets.
> Try to insolate [sic] the internal secretion of these to relieve glycosurea [sic].

Thus, with the seminal idea of Barron, began Banting's epoch-making experimentation with Best that led eventually to the discovery of insulin, which was first used on patients in Toronto General Hospital on January 11, 1922.

Banting subsequently gave credit to Barron, in a frequently quoted letter, for the original idea leading to isolation of insulin. Barron, in turn, paid personal tribute to Dr. Banting "as a man, for . . . he showed greatness in the way he unstintingly, in his writings and lectures, acknowledged the fact that his discovery followed the reading of my article. Such forthrightness is not to be taken for granted."

Moses Barron was born in Kovno, Russia, in 1883. His father emigrated to America, settling in Herman, Minnesota, where he later established his family, and where the young Moses Barron had his early schooling in a one-room schoolhouse in rural Minnesota. He entered medical school in the fall of 1905. After a six-year course, the young Dr. Barron became the first and sole intern at the University of Minnesota Hospital. For the next ten years he taught and did research in pathology. In 1917–1918, he saw service in France with the American Expeditionary Forces, returning to the United States as a major in the Medical Corps in 1919. In 1920 he forsook pathology for internal medicine, achieving the post of professor of medicine in 1933, a rank he held until his retirement in 1952, when he became professor emeritus of medicine. Dr. Barron was the first chief of medicine at the Mount Sinai Hospital in Minneapolis. After a long and distinguished career in Minnesota, Dr. and Mrs. Barron retired to Los Angeles in 1964.

Shortly after his arrival in Los Angeles, Dr. Barron became a consultant in the Department of Medicine at the Cedars-Sinai Medical Center, a title he held till his death in 1974 at the age of 92. Both in Minneapolis and Los Angeles, Dr. Barron was active in Jewish circles, and was a founder in the late twenties of the American Friends of the Hebrew University.

Cedars-Sinai at Los Angeles is proud to have had as a member of their staff in his later years this distinguished scientist who played a largely unsung but important role in the discovery of insulin and the eventual conquest of diabetes.

Diabetes Mellitus: Recent Developments in Treatment

Treatment, Complications, And Special Problems

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Update on Therapy of Diabetes Mellitus: Diet, Sulfonylurea Agents, and Insulin

MAYER B. DAVIDSON, M.D.

During the past five years, profound changes have occurred in the treatment of diabetes mellitus. These include:

- accumulating evidence that strict or tight diabetic control not only delays the microvascular complications of retinopathy and nephropathy as well as neuropathy, but also reverses early changes (1);
- acceptance of the critical role of home blood-glucose monitoring;
- new information challenging the recommended dietary guidelines (2);
- profusion of available insulin preparations (3);
- recent data challenging the accepted time course of action of regular insulin taken alone or in combination (4);
- introduction of two second-generation sulfonylurea agents (5);
- acceptance of near-euglycemia as a therapeutic goal in selected patients;
- possibility of combining insulin and sulfonylurea agent therapy in certain ketosis-resistant diabetic patients. The discussion here summarizes some of these new concepts and attempts to focus on utilizing this new information in a practical approach to treat the elevated glucose levels in diabetic patients.

Classification of Patients for Treatment

It is extremely important for treatment purposes to classify patients as either ketosis-prone (type 1) or ketosis-resistant (type 2). Ketosis-prone patients are virtually devoid of effective insulin and must therefore be treated with insulin. Ketosis-resistant patients retain some effective insulin and thereby avoid acidosis, even under stressful conditions. Approximately 25% of type 2 patients are treated by diet alone, 50% by sulfonylurea agents, and 25% by insulin. The usual approach is to try diet first, oral agents if diet fails, and finally insulin if the patient fails to respond to maximal doses of one of the more effective sulfonylurea compounds (Fig.)

Approximately 75% of ketosis-resistant (type 2) diabetic patients are diagnosed on either a routine physical examination or in the process of being evaluated for another condition. Most of the other 25% have few symptoms; all of these patients should be treated with diet alone first. I usually also give lean patients a trial of diet initially. If they fail to respond to diet alone, sulfonylurea treatment should be begun. The criteria for unsuccessful dietary management is 1–2 hr postprandial plasma glucose levels consistently exceeding 200 mg/dl. (Remember that whole blood glucose values are 15% less and adjust accordingly.)

Diet

Although diet is certainly a cornerstone of diabetic treatment, the general role of diet differs in patients taking insulin and those not taking insulin (Table 1). For a patient receiving insulin, the appropriate diet (4) is selected and the insulin regimen is adjusted accordingly. (The diet should not be manipulated to accommodate the insulin regimen.) Thus, meal timing and consistency must be fairly inflexible in these patients (patients taking multiple doses of insulin are an exception; see below). In contrast, patients not taking insulin have much more flexibility in meal timing and consistency. Of course, in all

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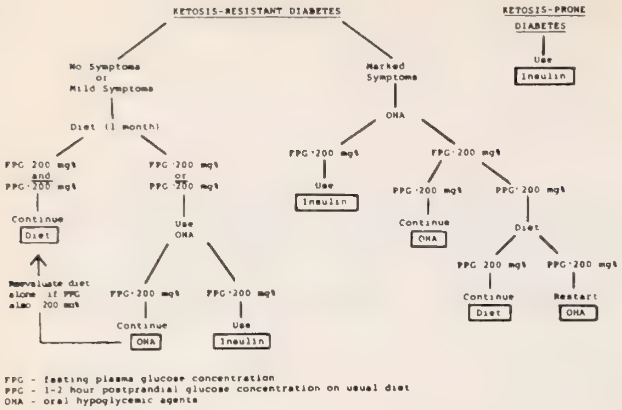
KETOSIS-RESISTANT DIABETES
KETOSIS-PRONE DIABETES
Use
Insulin
No Symptoms or Mild Symptoms
Marked Symptoms
Diet (1 month)
OHA
FPG 200 mg% and PPG ·200 mg%
FPG ·200 mg% or PPG ·200 mg%
FPG ·200 mg%
FPG·200 mg%
Use Insulin
PPG ·200 mg%
PPG· 200 mg%
Continue Diet
Use OHA
Continue OHA
Diet
Reevaluate diet alone if FPG also 200 mg%
FPG·200 mg%
FPG·200 mg%
PPG 200 mg%
PPG·200 mg%
Continue OHA
Use Insulin
Continue Diet
Restart OHA
FPG - fasting plasma glucose concentration
PPG - 1-2 hour postprandial glucose concentration on usual diet
OHA - oral hypoglycemic agents

Figure 1. General guidelines for management of diabetic patients who are ketosis-prone (type 1) and ketosis-resistant (type 2).

obese patients, hypocaloric diets are critically important for diabetic control whether the patients are receiving insulin or not; although exercise is an important modality of treatment for obese patients, it is ineffective unless accompanied by lowered caloric intake. Recent evidence suggests that lean diabetic patients with no history of obesity may be able to self-select their diet rather than learn and use the exchange system, as long as they avoid refined carbohydrates (6).

Although dietary recommendations for diabetic patients are generally agreed upon, current research continues to challenge them (4). High-fiber diets are beneficial but, frankly, many patients are unwilling to put up with the gastrointestinal side effects. It has recently been recognized that the form in which the carbohydrate is ingested will have a marked impact on the glucose rise after eating. Not only do various carbohydrate sources differ in their glycemic response; the same food will give a different result depending on how it is prepared. Furthermore, there is even recent evidence that sucrose may not be deleterious, especially if it is ingested in combination with other foods. What can be depended upon, however, is that dietary counselling belongs to the purview of dietitians. Although physicians have a role in ordering general dietary guidelines, we are often ill-equipped (in knowledge, time, and temperament) to provide specific dietary instructions.

Sulfonylurea Agents

All sulfonylurea (oral hypoglycemic) agents (5) work through similar mechanisms. They stimulate insulin secretion, both directly and by potentiating the effect of other insulin secretagogues. Importantly, they also potentiate the action of insulin in the peripheral insulin-sensitive tissues (liver, muscle, and fat). Although it was initially held that sulfonylurea agents accomplished this by increasing insulin binding, much recent evidence points toward a site of action beyond the receptor within the cell. Finally, they may also act directly on these tissues independently of insulin. Sulfonylurea agents should

TABLE 1

Dietary Strategies in Diabetic Patients Taking and Not Taking Insulin

Strategy	No insulin		Insulin	
	Nonobese	Obese	Nonobese	Obese
Decreased calories	No	Yes	No	Yes
Increased number of feedings	No	No	Yes*	Yes*
Day-to-day consistency				
Intake of calories	Not crucial	Not crucial	Important	Important
Carbohydrate content of each meal or snack	Not crucial	Not crucial	Important†	Important†
Timing of eating	Not crucial‡	Not crucial‡	Important†	Desirable†
Extra food for unusual exercise	No	No	Very important	Desirable§
Use of food to treat, abort, or prevent hypoglycemia	No‖	No‖	Very important	Very important

Modified with permission from West KM: Diet therapy of diabetes: an analysis of failure. Ann Intern Med 1973;79:425–434.

* Bedtime snack necessary if patients are taking intermediate- or long-acting insulin preparations. Some patients may also require snacks between meals, depending on insulin regimen.

† Less important for knowledgeable patients receiving multiple injections of regular insulin before meals or insulin pump therapy in whom adjustments in timing and amount of insulin is possible to accommodate more variable timing and carbohydrate content of meals.

‡ If possible, meals should be spaced 4 to 5 hours apart to allow postprandial glucose rise to return to preprandial levels.

§ Possibility of exercise-induced hypoglycemia may be less in obese patients because their level of exercise and sensitivity to insulin are both less than in nonobese patients.

‖ May be necessary for patients receiving sulfonylurea agents.

TABLE 2
Selected Properties of Sulfonylurea Agents

Generic name (trade name)	Tablet size (mg)	Usual daily dose range (mg)	Maximal dose (mg)	Duration of action (hrs)
First-generation compound				
Tolbutamide (Orinase)	250, 500	500–2,000 (divided)	3,000	6–12
Chlorpropamide (Diabinese)	100, 250	100–500 (single)	750	60
Acetohexamide (Dymelor)	250, 500	250–1,500 (single or divided)	1,500	12–24
Tolazamide (Tolinase)	100, 250, 500	100–750 (single or divided)	1,000	12–24
Second-generation compound				
Glyburide (Micronase, Diabeta)	1.25, 2.5, 5.0	2.5–10 (single or divided)	20	12–24
Glipizide (Glucotrol)	5.0, 10.0	5–25 (single or divided)	40	10–24

only be used in type 2 diabetic patients. They are ineffective in type 1 patients.

Choosing the Agent

The sulfonylurea agents available to physicians in the United States (Table 2) include four first-generation compounds available here for over 15 years and two second-generation agents available in the United States since May 1984 (they have been used for many years in Europe).

Which one is the best agent to use? There is no clear-cut answer; I would suggest four criteria that physicians should weigh to select a drug over similar agents (for all treatment decisions, not just for sulfonylurea compounds): effectiveness, side effects, ease of compliance, and cost.

Effectiveness. In regard to effectiveness I am not speaking of potency, that is, what amount of drug is necessary to achieve the desired results. Clinically, that is irrelevant. What is important is effectiveness—in this case, what proportion of type 2 patients who have failed diet can be controlled by one agent versus another, or, a more stringent test, what proportion of patients failing on maximal doses of one agent can be rescued on another. Combining the published literature with my personal extensive experience with acetohexamide, the following guidelines seem appropriate:

Tolbutamide is the least effective of the sulfonylurea agents and acetohexamide lies between tolbutamide and chlorpropamide. Chlorpropamide, tolazamide, glyburide, and glipizide are equally effective. If a patient fails on maximal doses of one of these four agents, there is approximately a 10% chance of succeeding with one of the other three.

Side Effects. Less than 5% of all patients experience side effects with sulfonylurea agents. Gastrointestinal and dermatological reactions are by far the most common. Chlorpropamide, but not the others, can cause the alcohol-flushing syndrome which may occur in 10%–30% of patients. Additionally, chlorpropamide can cause hyponatremia via the syndrome of inappropriate antidiuretic hormone secretion. This is most likely to occur in older patients also receiving thiazide diuretics. Hypoglycemia will obviously occur with all of them, especially in patients who eat irregularly, as some older patients tend to do. Although sulfonylurea-agent-induced hypoglycemia may last for several days regardless of the inciting drug, it may last longer with chlorpropamide, which has an extensive duration of action. Reversible intrahepatic cholestasis leading to obstructive jaundice is a rare side effect, but it seems to be more common with chlorpropamide. Finally, these drugs do not have deleterious effects on the cardiovascular system, in spite of the contention of the University Group Diabetes Program (UGDP) study. The assertion of deleterious effects was not borne out by further analysis of their data or by six additional studies (5).

Compliance. Remembering to take the pills is the only issue of compliance with these agents. Tolbutamide is inactivated rapidly in the liver and must therefore be taken at least twice and sometimes three times a day. Tolazamide, glyburide, and glipizide are also degraded to mostly inactive products in the liver, but apparently at a slower rate. The first half of a maximal dose of these drugs is usually given before breakfast (500 mg of tolazamide, 10 mg of glyburide, and 20 mg of glipizide). If greater amounts are needed, they are usually taken before supper. Acetohexamide is also rapidly changed in the liver, but the resulting product is 2.5 times as active as the parent compound, and thus the timing of its biological effect is similar to tolazamide, glyburide, and glipizide. The first gram of acetohexamide is taken before breakfast, the remaining 500 mg

TABLE 3
Recommended Initial Doses of Sulfonylurea Agents for Ketosis-Resistant Patients with Diabetes Mellitus

	Asymptomatic diet failures*		Marked-symptom pts‡
	FPG <200 mg/dl	FPG >200 mg/dl†	
Tolbutamide	500	1000	—
Acetohexamide	250	500	—
Tolazamide	100	250	1,000
Chlorpropamide	100	250	750
Glyburide	1.25	2.5	20
Glipizide	2.5	5.0	40

Abbreviation: FPG, fasting plasma glucose concentrations.

* Relatively asymptomatic patients after initial treatment with diet alone.

† For patients over 65 years of age, use dose for younger patient with FPG <200 mg/dl.

‡ For patients over 65 years of age, use dose for younger asymptomatic patient with FPG >200 mg/dl. Increase quickly after 1 week if no response seen.

before supper. Chlorpropamide is partially metabolized in the liver but the metabolites must also be active, since the biological effect of the drug can last up to 60 hours. Therefore, chlorpropamide need only be given once a day, usually before breakfast. The relationship between drug and meal ingestion is unimportant except in the case of glipizide, which seems to be more effective if taken at least 30 minutes before eating.

Therefore, from the point of view of compliance, chlorpropamide would be the drug of choice, since it never has to be taken more than once a day. This must be balanced by the realization that it has more side effects than the other sulfonylurea agents. I usually do not use chlorpropamide as the initial drug in patients over 65 years because of the risk of both hyponatremia and prolonged hypoglycemia in this age group.

Cost. Although cost is an important consideration, it is difficult to generalize since cost varies from locale to locale. Prices quoted by pharmaceutical companies usually refer to cost to the pharmacist; price to the patient varies because of uneven markups by the pharmacy. A phone call to the patient's pharmacy is the only accurate way to determine what these drugs will actually cost. Thus, there are no clear-cut cost advantages of one sulfonylurea agent over another.

Clinical Dosage Guidelines

Asymptomatic Patients. The criteria for the initial dose of sulfonylurea agents for asymptomatic patients (Table 3) may be different for patients under and over 65 years of age. For those under 65, the fasting plasma glucose concentration (FPG) determines the initial dose. If the FPG is under 200 mg/dl, a small dose is used; if it is over that amount, a larger dose is recommended. All patients over 65 years of age should be started on a small dose since they seem to be very sensitive to these agents. Patients should be evaluated every week or two. The FPG is relatively consistent in type 2 patients not receiving insulin. If it exceeds 200 mg/dl, it should be followed to ascertain the efficacy of the sulfonylurea agent. The dose is gradually increased until one of two things occurs:

- a maximal dose (Table 2) is reached and the FPG is still over 200 mg/dl: the patient is a candidate for insulin therapy. Switching to the maximal dose of another effective agent (chlorpropamide, tolazamide, glyburide, or glipizide) may be helpful in a few patients.
- FPG drops below 200 mg/dl: postprandial level is followed. The goal here also is to reduce this value to below 200 mg/dl, and the dose of the sulfonylurea agent is gradually increased until one of two things happens:

—1–2 hour postprandial value falls below 200 mg/dl. At this point the dose of the drug should be lowered (especially if the patient is losing weight) to determine if perhaps diet alone may become effective. (Patients should not be exposed to drugs unless necessary.)

—maximal dose of the drug is reached and the postprandial glucose concentration remains over 200 mg/dl (assuming the FPG is under 200 mg/dl). At this point the drug regimen is maintained unless tolbutamide or acetohexamide is being used. In that case, switching to one of the other four agents may improve diabetic control.

Symptomatic Patients. Occasionally, ketosis-resistant (type 2) diabetic patients will have marked symptoms of uncontrolled diabetes: polyuria, polydipsia, polyphagia, and weight loss. Many physicians opt to give these patients insulin. However, one can often treat them effectively with sulfonylurea agents. A maximal dose (Table 3) of one of the four most effective agents should be used. Within a week, it will be apparent which patients are not responding and should therefore be switched to insulin therapy.

Many patients' symptoms will disappear, especially if an appropriate diet is followed; these patients can then be managed in the same manner as the asymptomatic patients. That is, if their FPG stabilizes above 200 mg/dl, insulin is then started. If the FPG falls below 200 mg/dl but the postprandial value remains above 200 mg/dl, maximal doses of the sulfonylurea agent are maintained. If 1–2 hour postprandial glucose levels drop beneath 200 mg/dl, the dose of the sulfonylurea is gradually reduced to determine if dietary management alone may be suitable. I have seen such a response in these patients, especially in obese persons on hypocaloric diets who continue to lose weight. In this manner, some markedly symptomatic patients can avoid unnecessary insulin therapy (with its attendant tremendous change of life style); should maximal doses of sulfonylurea agents be inadequate, the delay in beginning insulin therapy is short.

Other Considerations

Some final points. First, a few drugs will potentiate the effects of sulfonylurea agents by displacing them from serum albumin to which they are bound. The most important such drugs are the sulfonamides. Others used less frequently are chloramphenicol (Chloromycetin), clofibrate (Atromid-S), bishydroxycoumarin (Dicumarol), phenylbutazone (Butazolidin), and oxyphenbutazone (Tandearil). Second, using two sulfonylurea agents together is inappropriate; there is no additive benefit.

Third, in my view, the available data do not make a very strong case of combining insulin and sulfonylurea agent therapy. In the majority of studies, no benefits have been achieved over those noted with insulin alone. In the few in which control was improved, the improvement was only modest. One must weigh the additional expense involved and also the fact that increased amounts of insulin would have achieved the same if not better results.

Fourth, I believe that if obese patients fail sulfonylurea agent therapy, they should be treated with insulin. Although it is often argued that this may cause them to gain more weight (the evidence is conflicting on this point), a few extra pounds adds little additional health risk compared to the known (eventual) devastating effects of hyperglycemia.

Flexibility in Management. One final comment: The cutoff value of 200 mg/dl, both in the fasting state and 1–2 hours after eating, is only a guide to aid the clinician in deciding among the various therapies available for patients with diabetes mellitus. If the renal threshold is relatively normal (which, of course, is not always the case), and if chemical measurements of blood sugar are not available, persistent glucosuria can be substituted for the plasma glucose value of 200 mg/dl. I use the value of 200 mg/dl only in deciding to *change* therapy. I attempt to obtain plasma glucose concentrations as near normal as possible without subjecting the individual to the risk of frequent or profound hypoglycemia. For instance, if a diabetic patient who takes insulin maintains an FPG concentration between 175 and 200 mg/dl, I will increase the dose in order to lower this value to less than 150 mg/dl. Similarly, if a patient taking 500 mg of tolazamide consistently has FPG and/or postprandial levels between 150 and 200 mg/dl, I will increase the dose to 750 mg in an attempt to decrease both values to less than 150 mg/dl. If this patient had been taking maximal doses of tolbutamide or acetohexamide, I would substitute full doses of one of the other sulfonylurea agents, the choice initially influenced by the age of the patient.

Insulin

Although insulin (2, 3) has been used in medical practice for over sixty years, physicians now face new complexities in prescribing insulin. First, over 40 preparations are now available. Second, there is new information on the timing of action of regular insulin, both singly and in combination with certain intermediate- and long-acting insulin preparations. Third, a new emphasis on achieving near-euglycemia in many patients receiving insulin requires innovative insulin regimens to preserve a flexible and quality life style. I summarize here information that should allow the physician to design an appropriate insulin regimen for individual patients and guide him/her among the claims and counterclaims for various insulin preparations.

Timing of Activity. The most important characteristic of insulin preparations is their time course of action—onset, peak, and duration. These relationships (summarized in Table 4) are independent of pharmaceutical manufacturer, species source, and degree of purity. I must emphasize that our methods of evaluating insulin absorption are crude, and that timing variability is wide, not only from patient to patient, but unfortunately also from day to day in any one patient; such day-to-day variation has been estimated to reach 25%.

In addition, a significant number of patients have a delayed response to regular insulin; in these individuals, the time-course of this short-

TABLE 4
Approximate Time-Activity Relation of Various Insulin Preparations

Insulin activity type	Onset (hrs)	Peak (hrs)	Total duration (hrs)
Short			
Regular*	0.5–1	2–4†	4–6
Semilente	1–2	3–6	8–12
Intermediate			
NPH‡	3–4	10–16	20–24
Lente	3–4	10–16	20–24
Long			
PZI§	6–8	14–20	>32
Ultralente	6–8	14–20	>32

* Also called crystalline zinc insulin (CZI).

† In some patients, regular insulin may peak later (4–8 hr) and last considerably longer; addition of regular to intermediate-acting insulin may cause afternoon hypoglycemia in these patients.

‡ Neutral protamine Hagedorn.

§ Protamine zinc insulin.

acting insulin is similar to semilente insulin. The characteristic clinical response to regular insulin (which should be injected 30 minutes before eating) in these patients is a high 1–2 hour postprandial glucose value and a low glucose value before the next meal 4–5 hours later. Should this situation occur, the patient should take regular insulin 60–90 minutes before eating, if at all feasible.

Finally, regular insulin added to lente or ultralente insulin in the same syringe will have a delayed response in all patients. Apparently, the excess zinc in the lente series of insulins binds the regular insulin and retards its absorption. Thus, when using combinations of short- and intermediate-acting insulins, regular should be added to NPH insulin. If short- and long-acting insulins are used together, regular has to be added to ultralente insulin or be injected separately. Although absorption of the regular insulin will be delayed somewhat if mixed with ultralente insulin, the PZI preparation contains excess protamine, so that little short-acting insulin will be available until the ratio of regular to PZI exceeds approximately 1:1.

Species Source and Cost. Once the type or types of insulin—short, intermediate, and long-acting—has been chosen, four other factors to consider are concentration, purity, species source, and cost. Over 90% of all insulins sold are U-100; U-40 is used mostly in children who usually need lower doses. Although differences in purity used to be important because of cost and immunologic side effects, purity is no longer a major consideration. The Federal Drug Administration has recently mandated that all insulin preparations sold in this country must be of a purity that was matched by only the most pure preparations several years ago. Thus we are left with species source and cost as the major factors.

Beef insulin differs from human insulin by 3 amino acids, and pork insulin differs from human by only one. This is probably the reason that beef insulin is more antigenic than pork insulin in patients. That is, IgG antibodies that bind insulin are formed in higher titers against beef insulin. However, both pork and human insulin itself will cause low titers of IgG insulin-binding antibodies in patients. The titers are slightly higher in individuals taking pork insulin than in those taking human insulin, but these "higher" titers are extremely low compared to the response to the older impure insulins. Furthermore, the clinical significance of these small titers of insulin-binding antibodies is unknown. Therefore, the most important consideration is cost, which depends on the local pharmacy.

If one selects human insulin, there is an important consideration to bear in mind. Although most studies reported no differences between the time course of human and pork insulin, a few found a more rapid onset, peak, and duration of action for human insulin. It seems that in some patients human insulin will work faster than pork or beef insulin. This possibility must be kept in mind when patients are switched to or started on human insulin.

Effectiveness and Home Monitoring. In regard to using insulin effectively, sensitivity to exogenous insulin in diabetic patients can vary over time. This happens in the absence of a recognizable cause such as infection, weight change, or emotional stress and occurs more often in type 1 diabetic patients. For this reason, insulin regimens must usually be evaluated, and insulin doses changed, much more frequently than every few months, either by the physician or by the patient under the doctor's guidance. This requires ongoing patient-collected information on the degree of diabetic control.

The more often patients perform home glucose monitoring (or even urine testing), the tighter their control will be. Under ideal circumstances, the physician needs home blood glucose monitoring results 7 or 8 times a day—before and after each meal and before the bedtime snack. Occasionally a 3 AM value is also necessary, especially when insulin doses affecting overnight glucose homeostasis are changed. Since this amount of home monitoring is unrealistic for most patients, I describe here an approach that basically uses four bits of information per day but allows decisions to be made with less data as well.

The actual times throughout a 24-hour period during which each type of insulin is effective and the timing of the tests reflecting that activity are summarized in Table 5. Six insulin regimens, labeled A through F, for achieving tight control are summarized in Table 6. In regimen E, some diabetologists prefer to give one half of the ultralente insulin in the morning and the other half in the evening. The fasting test is still used to regulate the amount of ultralente insulin, and both doses are changed concurrently. In general, I split the dose of ultralente when the amount exceeds 20 U. Regimen F, insulin infusion pump therapy, is included for completeness and for comparison to the other approaches. In my view, only physicians experienced with this mode of therapy and who will devote the extra amount of time that it requires should supervise patients on pump therapy.

The degree of diabetic control is measured by glucose concentration (Table 7) corresponding to the values represented by the colored chart on a Chemstrip vial or the values half-way between the two. (Chemstrips are one of the strips used for home blood glucose monitoring which can be read visually as well as by several meters.) Most patients are able to judge if the developed color on the strip is very near one of the listed values or is approximately half-way in between. For those using meters, 200 mg/dl should be substituted for 210 mg/dl.

To start lean patients (under 125% of ideal body weight) on insulin using either regimens A or B, I initially give 10 U of NPH in the morning and 4–5 U in the evening. For obese patients (over 125% of ideal body weight), the initial doses are 20 U of NPH in the morning and 10 U in the evening. The doses are increased gradually until level 1 of control (Table 7) is reached before breakfast and supper. At that point, the need for regular insulin is assessed by evaluating the before-lunch and before-bedtime-snack glucose values. The initial dose is 4 units in lean patients and 8 units in obese ones. These amounts are gradually increased until level 1 of control (Table 7) is reached. Further increases in both intermediate- and short-acting insulin (or, put another way, attaining more strict diabetic control) should be accomplished in the patient's usual home environment, not the hospital. Eating, activity, and emotional patterns are usually quite different in the two settings. Tight hospital control can lead to hypoglycemia at home.

To start regimens C, D, and E, which utilize regular insulin before each meal, I initially use 5 U for lean patients and 8–10 U for obese patients. The initial dose of NPH and ultralente insulin in these regimens is 10 U for lean and 16 U for obese individuals. All of the doses are then adjusted depending on test results. If insulin therapy is begun in the hospital utilizing regimens C, D, or E, the same caveat as for regimens A and B applies: The final insulin adjustments must be made in the patient's typical daily environment. If patients are switched from regimens A or B to regimen C, D, or E, the old insulin dose

TABLE 5

Period of Glucose Control by Type of Insulin and Timing of Tests of Activity

Insulin	Time injected	Period of activity	Test timing
Regular	Before a meal	Between that meal and either the subsequent one or the bedtime snack (if insulin taken before supper)	Both following meal before which insulin is injected and before subsequent meal or bedtime snack (if insulin taken before supper)
NPH	Before breakfast	Between lunch and supper	Before supper
NPH	Before supper or before bed	Overnight	Before breakfast
Ultralente	Before breakfast	Overnight	Before breakfast

NPH, neutral protamine Hagedorn.

TABLE 6

Six Insulin Regimens for Achieving Strict Diabetic Control

Regimen	Before breakfast	Before lunch	Before supper	Before bed
A	NPH/regular*	—	NPH/regular	—
B	NPH/regular	—	Regular	NPH
C	Regular	Regular	NPH/regular	—
D	Regular	Regular	Regular	NPH
E	Ultralente/regular	Regular	Regular	—
F	Insulin pump: small amount of regular insulin infused throughout 24-hr period (basal) with boluses of regular insulin given before each meal			

* Regular insulin usually injected 30 min before designated meal.

TABLE 7
Degrees of Diabetic Control in Order of Increasing Strictness

	Glucose concentration
1. Before meal and bedtime snack	≤180 mg/dl
2. Before meal and bedtime snack	≤150 mg/dl
3. Before meal and bedtime snack	≤120 mg/dl
4. One- to two-hr post-meal	≤210 mg/dl*
5. One- to two-hr post-meal	≤150 mg/dl

* ≤200 mg/dl if meter is used.

may provide clues for the new one such that the initial starting doses discussed above may not be appropriate.

Retrospective Monitoring. Because sensitivity to insulin is not consistent, insulin doses often need to be changed to achieve and maintain tight diabetic control. Algorithms for adjusting insulin doses are based on retrospective data, that is, insulin doses are changed in response to three-day indices of control (Table 8) or, when indication of need to change insulin dosage is not clear after three days, a week-long trend in test results (Table 9). Effective use of this approach requires a relatively consistent pattern of diet and exercise. Many patients can be taught to adjust their insulin doses prospectively, an approach which usually yields better control; this approach is discussed below.

Many patients, of course, are unwilling to consistently perform home blood glucose monitoring four times a day. Since ideally the minimum information concerning diabetic control needs to reflect the time between breakfast and lunch, lunch and supper, supper and bed, and overnight (four times per 24-hour period), a urine test for glucose may be substituted for the blood glucose value before a meal or at bedtime. A first-voided urine should be tested since it reflects a large part of the period in which we are interested in ascertaining the degree of control. Any positive result is considered "unsatisfactory" (the target level has been exceeded), and a negative test must be considered "satisfactory" (the target level has been met). Urine tests for glucose are really not suitable to monitor patients who are striving for tight control, since positive results often appear only when blood glucose values exceed the least strict degree of control (level 1 in Table 7). However, some information is better than none, and many patients can usually be persuaded to provide the physician with a combination of blood and urine values.

Certain caveats must be kept in mind with each of the regimens. In regimens A and B, patients have the least flexibility with regard to the timing and content of meals. Hypoglycemia is most likely to occur with these two regimens if meals are delayed.

In regimens A and C, the intermediate-acting insulin given before supper may have peak activity in the middle of the night rather than toward morning in some patients. In this situation, increasing the dose may lead to hypoglycemic reactions during the middle of the night before the target level of glucose before breakfast is achieved. If this should occur, switching the intermediate-acting insulin to before bedtime (regimen B) should solve the problem.

In regimens C and D, if the period between lunch and supper is too prolonged (usually greater than 5–7 hours), the blood sugar before supper may be too high because the effect of the regular insulin given before lunch may have worn off.

In regimen E, since ultralente insulin starts to work 6–8 hours after injection, hypoglycemia may occur between lunch and supper, especially if supper is eaten late. This is usually not a problem when the dose of long-acting insulin is low (approximately 10 units) but may become a problem at higher doses.

In regimen F, patients utilizing insulin pumps (which use only regular insulin) have no intermediate- or long-acting insulin available; hence interruption of these subcutaneous infusions (usually due to difficulties with needle or tubing) can lead to hyperglycemia, and to ketosis in type 1 patients, within 6 to 8 hours.

Finally, with any regimen that does not routinely measure urinary ketone bodies, this test must be utilized whenever type 1 patients are sick. Many patients who rely exclusively on home blood glucose monitoring prefer not to test their urine at all. However, since diabetic ketoacidosis can often occur with blood sugars below 300 mg/dl (7), physicians must insist upon urine testing for ketone bodies under these circumstances.

A glucose value during the middle of the night (about 3 AM) is helpful under two circumstances. The first is to determine whether unrecognized hypoglycemia at this time is causing rebound fasting hyperglycemia (the Somogyi phenomenon); in my view, this occurs very infrequently. The second situation is the recently recognized "dawn phenomenon." Apparently insulin sensitivity decreases during the period from 4 AM to 9 AM compared to the evening and early hours

TABLE 8

Algorithm for Adjusting Insulin Doses Based on Retrospective Data (3-Day Rule)

1. Select one of the first three levels of diabetic control desired.*
2. If blood glucose is greater than upper target level at same time of day for 3 days in a row, increase dose of the appropriate insulin by 1 to 2 units† as follows:

If before-breakfast test too high:

Regimen	Insulin
A	NPH—before supper
B	NPH—before bed
C	NPH—before supper
D	NPH—before bed
E	Ultralente—before breakfast
F	Increase basal rate by either 0.1 U/hr or 2 U/24-hr

If before-lunch test too high:

Regimen	Insulin
A through E	Regular—before breakfast

If before-supper test too high:

Regimen	Insulin
A and B	NPH—before breakfast
C through E	Regular—before lunch
F	Bolus—before lunch

If before-bedtime snack‡ too high:

Regimen	Insulin
A through E	Regular—before supper
F	Bolus—before supper

3. If blood glucose is <70 mg/dl§ at same time of day for 3 days in a row, decrease dose of the appropriate insulin as in no. 2 above.
4. A mild hypoglycemic reaction (which is easily treated) for no apparent reason (no delay of meal, same amount of food, no increase in exercise, no error in insulin dose) counts as a <70 mg/dl blood glucose value before the next meal even though the glucose value measured at that time will probably be high. For example:

Time of reaction	Meal to which <70 mg/dl should be assigned
Between breakfast and lunch	Lunch
Between lunch and supper	Supper
Between supper and bedtime	Bed
Between going to bed and arising	Breakfast

5. If a severe hypoglycemic reaction for which there is no apparent reason occurs, the appropriate insulin dose should be decreased as shown in no. 2 above the very next time it is to be given.
6. Once the desired level of diabetic control is consistently achieved, consider advancing to the next level of increasing strictness (Table 7).
7. For the 4th and 5th levels, glucose concentrations between 1 to 2 hours following meals must be measured. If these values exceed the upper target level for 3 days in a row (assuming consistency in the size of the meals), increase the dose of the regular insulin taken before that meal.

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* See Goals of Therapy for which level to select initially.

† 3 to 4 units may be more appropriate in obese patients (>125% of ideal body weight; see reference 4 for calculation of ideal body weight).

‡ Bedtime snack not necessary for regimen F; however, test at this time still needs to be done to evaluate response to before-supper bolus dose.

§ For patients using Chemstrips, color nearer the midrange between 40 and 80 mg/dl is considered <70 mg/dl; color nearer the 80 mg/dl value is not.

of the night. Measurement of AM glucose values is particularly important in patients on insulin pump therapy who are usually receiving a constant amount of insulin overnight (via the basal rate). One needs to be assured that in an effort to achieve fasting euglycemia, the patient is not experiencing hypoglycemia unrecognized during sleep, since the constant basal rate would be more effective at this time than before breakfast. Thus, when changes are made in the basal rate, it is advisable for the patient to ascertain that the glucose concentration is not falling too low in the middle of the night. (If that occurs, some insulin pumps are able to change the basal rate automatically at a preset time.) This same principle applies in general to other modes of insulin therapy. However, since constant amounts of insulin are not delivered by injected insulin, the timing between the injections and the test would be so important that interpretation of the results would be difficult. In practice, the day-to-day response of patients to insulin varies so much that routine monitoring in the middle of the night in patients not on pump therapy does not seem justified unless one suspects unrecognized hypoglycemia.

With appropriate encouragement from their physicians, nurse educators, and/or support groups, many patients will carry out monitoring four times a day. To minimize the time spent on the phone, every effort should be made to teach these algorithms to the patient to the degree to

TABLE 9

Algorithms for Adjusting Insulin Doses Based on Retrospective Data (7-Day Rule)

1. Use at end of each week only if no change had been made using 3-day rule in that particular component of insulin dose.
2. If number of test results greater than desired value minus number of test results <70 mg/dl* and unexplained episodes of hypoglycemia is 4 or greater, increase appropriate component of insulin dose by 1 or 2 units.†
3. If number of test results <70 mg/dl* and unexplained episodes of hypoglycemia minus number of tests results above desired level is 4 or greater, decrease appropriate component of insulin dose by 1 or 2 units.†
4. If criteria of no. 2 or no. 3 not met, no change of insulin dose.

* Value may be higher for older patients, those who experience hypoglycemia without symptoms and those with autonomic neuropathy.

† 4 units may be more appropriate in obese patients.

which the patient is capable of mastering them. Some may have no difficulty; others may be able to use the 3-day rule only; still others can only handle adjusting one or two components of the insulin regimen, rather than all of them. Once patients are able to follow some or all of these algorithms, I have them mail their results to me at appropriate intervals (every week or two initially, and every month or two eventually) so that the results can be evaluated and the patient contacted at convenient times in my schedule. If patients monitor less often, I have them keep a record and send it to me every month. In that manner, I am able to adjust their insulin doses based on an aggregate of data collected over a shorter period than the 3 to 6 months between office visits. If resources are available, a nurse can be taught how to use these algorithms, thus saving much physician time.

Postprandial Values. Two extensions of the approach described above often lead to better control. The first is to attempt to achieve 1- or 2-hour postprandial values under 200 mg/dl (level 4, Table 7) and, if that is successful, values under 150 mg/dl (level 5, Table 7). One simply uses these postprandial values in the algorithms instead of the preprandial ones. The glucose concentration considered too low postprandially should be 100 mg/dl rather than the preprandial concentration of 70 mg/dl.

Prospective Monitoring. The second extension is to use prospective data to decide the amount of each injection of regular insulin. The dose of that part of the insulin regimen reflected in the fasting test is still determined by the retrospective method described above. However, the amount of regular insulin injected before each meal is composed of three components: the *basic dose* the patient takes routinely, adjusted according to the algorithms already described, and two adjustments.

The first of the two adjustments is a *compensatory dose,* based on the prevailing blood glucose value just prior to the insulin injection, and varying widely from patient to patient. Two decisions have to be made: (a) what range of blood sugars should be used for each compensatory dose, and (b) how much insulin should be assigned to each range. The final answers are always arrived at empirically. A suggested approach is to use the easily discernible Chemstrip ranges (80–120, 120–180, 180–240, 240–400, and greater than 400 mg/dl). The amount of extra insulin for each range is related to the patient's total basic dose—the less insulin the patient takes, the smaller the extra amount. I usually subtract a few units of insulin for preprandial values less than 80 mg/100 ml. The patients in our diabetes program have compensatory doses ranging from −2 to +10 units for various blood sugar values. After experience is gained by each patient, adjustments of both the ranges of blood sugar and extra amounts of insulin for each range are frequently made. Our patients taking morning NPH insulin (regimens A or B), and therefore performing home blood glucose monitoring before breakfast and supper, often use these values to take compensatory doses of regular insulin before these meals. In this situation, they are using prospective data only part of the time.

An advantage of using prospective results is that if a preprandial value is high (and the patient's schedule permits), the meal can be delayed so that the preprandial insulin will have an opportunity to lower the glucose level before the ingested food raises it again. The postprandial glycemia will thus be less than if the meal had been eaten on time.

The second of the two adjustments is the *anticipatory dose.* Some patients attempt to judge the amount of food (it should be the carbohydrate content) in the upcoming meal and adjust their insulin accordingly. As one might expect, this seldom leads to a decrease in insulin, because most patients attempt to compensate for extra food. The anticipatory component is not used by most of our patients, but those who do usually underestimate and end up too high before the next meal.

Achieving Patient Participation. The limiting factor for monitoring patients who take insulin is the amount of information that they will furnish. The physician should continually encourage patients to increase the frequency of their home blood glucose monitoring, to start it if they are relying only on urine testing, or to embark on urine testing if they are not monitoring themselves at all. Diabetes educators and patient-support groups are often important factors in patient acceptance of more vigorous attempts to achieve better diabetic control. It frequently takes me months to several years to persuade patients to monitor themselves appropriately. Continued elevated glucosylated hemoglobin values motivate some patients to undergo the discipline of home blood glucose monitoring. Once they start, the physician's approach obviously has to be tailored to the frequency of the patient's testing. The guidelines described above are just that—guidelines. Decisions about when and how to change insulin doses can be flexible within these general principles.

Goals of Therapy

Which level of control to aim for, at least initially, is influenced by (a) the age of the patient, (b) whether the patient has type 1 or type 2 diabetes, (c) the length of time type 1 patients have had diabetes, (d) the patient's awareness of hypoglycemic symptoms, and (e) the clinical evidence for autonomic neuropathy.

Understanding the hormonal response to hypoglycemia in normal subjects and diabetic patients is important for arriving at this decision. In normal and type 2 diabetic individuals, four hormones are secreted in response to hypoglycemia. Glucagon and the catecholamines, epinephrine and norepinephrine, are released rapidly and have an immediate effect in restoring the blood sugar toward normal. The secretion of growth hormone and cortisol is delayed, and their anti-insulin effect does not occur immediately but is long-lasting. Selective blockade of each of these hormones during hypoglycemia revealed that (a) as long as glucagon was secreted, glucose levels were restored normally; (b) if glucagon was absent but the catecholamines were present, restoration was delayed but eventually occurred; (c) growth hormone and cortisol secretion was unnecessary for return of glucose levels to normal (at least in the short term), and (d) if both glucagon and catecholamines were absent, glucose concentrations remained at the nadir levels.

This latter observation becomes extremely important in type 1 patients because within a year or two of diagnosis the glucagon response to hypoglycemia is impaired even though glucagon is hypersecreted in these patients under other circumstances. By four years after the diagnosis, the glucagon response is minimal. Furthermore, the catecholamine response to hypoglycemia is also blunted after five years of type 1 diabetes even in the absence of clinical autonomic neuropathy. Thus, in type 1 patients who have had their diabetes for greater than five years, there is a good chance that secretion of both of the critical hormones necessary to respond to hypoglycemia is either absent or impaired. Secretion of the counterregulatory hormones remains either intact or nearly so in type 2 diabetic patients.

Clinical Choices. Therefore, among patients regularly performing home blood glucose monitoring, level 1 of diabetic control is selected for the following: (a) type 1 patients with diabetes of greater than five years' duration, (b) any patient who experiences hypoglycemia without concomitant signs and symptoms, (c) any patient with clinical evidence of autonomic neuropathy, and (d) any patient taking insulin over 65 years of age. If preprandial values under 180 mg/dl can be achieved without inordinate difficulties with hypoglycemia, the target range is carefully advanced to level 2 for all of these groups except patients over 75 years of age. Because of their more limited life expectancy and the increased danger of hypoglycemia due to age-associated coronary artery and cerebrovascular disease, level 1 is maintained in these patients. Patients between 65 and 75 years of age have a longer life expectancy, and therefore I attempt to advance them carefully to level 2. This target level, preprandial values under 150 mg/dl, is the initial goal in all other groups of patients except those who begin insulin therapy in a hospital. Patients with autonomic neuropathy, and especially those who experience hypoglycemia without premonitory signs and symptoms, as well as those between 65 and 75 years are kept at level 2. All other patients who are able to achieve level 2 without too much difficulty with hypoglycemia are carefully advanced to level 3 (preprandial values under 120 mg/dl). Levels 4 and 5 require measuring blood glucose concentrations postprandially and are attempted in only a small minority of patients—unfortunately.

Important factors in achieving tight control in insulin-requiring patients are relatively constant patterns of eating (unless the patient has mastered the appropriate amount of anticipatory insulin to use) and exercise and a stable emotional state. In controlling diabetes with insulin, a balance must always be achieved between attempting to return glucose concentrations to near euglycemia and the risk of hypoglycemia. Under the present relatively crude system of replacing or supplementing endogenous insulin with exogenous insulin, some episodes of hypoglycemia are almost unavoidable if glucose concentrations are to approach normal most of the time. Since tight control has such important benefits (1), I ask my patients to tolerate occasional (2 to 3 weekly) mild episodes of hypoglycemia. However, if these episodes occur more frequently, are very distressing to the patient, are not quickly aborted, and most importantly, are not easily recognized, I reduce the insulin dose and settle for the level of control in Table 7 less strict than the one at which these difficulties occurred.

These same principles apply to controlling patients who furnish the physician with more sporadic data (e.g. glucose concentrations several times a day, two to four times a week). If one can assume that these data represent relatively consistent values, insulin doses can be adjusted accordingly. However, if the glucose levels are not truly representative, hypoglycemia may become a problem, and one has to decrease insulin doses and settle for looser control.

In patients who only perform urine testing, the goal of therapy is no glucosuria in all first-voided urine samples. Initially, preprandial urines are tested, and once they become negative for glucose routinely, postprandial urine should be used. In patients with an increased renal threshold for glucose, even negative urine tests do not ensure very good control. Conversely, in the rare (nonpregnant) patient with a lowered threshold for glucose, negative urine test results may be associated with unacceptable hypoglycemia.

Although a discussion of the background and use of glucosylated (glycosylated) hemoglobin (Hgb) levels is beyond the scope of this paper, the goal of therapy in regard to this test obtained every two to three months can be simply stated: to achieve normal values. However, the closer one is to normal, the more hypoglycemia insulin-requiring patients experience. Therefore, a balance must be struck between the two. In practice, since glucosylated Hgb values do not guide day-to-day therapeutic decisions, those values are used to help decide whether more determined efforts need to be made to optimize control. Sometimes patients are doing the best they can and improvement is not possible. Many patients, however, are able to improve their control (or actually their compliance with the prescribed therapeutic regimen, yielding better control) and glucosylated Hgb levels serve as the reminder and motivation.

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Overnutrition in the Diabetic Patient

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The principal malnutrition problem in the United States today is obesity (overnutrition). Being anything from pleasantly plump to overtly corpulent has from time to time been associated with wealth, power, beauty, even good health; however, in the past decade or so, the pathological conditions exaggerated by obesity have been documented. Interestingly enough, Hippocrates (1) many centuries ago noted that "sudden death is more common in those who are naturally fat than in the lean."

Obesity is an excess of body fat that frequently results in a significant impairment of health. The excess fat accumulation is normally associated with increased fat cell size; however, the number of fat cells is also increased in extreme obesity. Genetic and environmental factors include excess calorie intake, decreased physical activity, and metabolic and endocrine abnormalities.

The modern and Western way of eating, in combination with a significant historical change in lifestyle behaviors, has produced an increasing amount of obesity. Around the turn of the century, approximately 5% of the adult population in the United States was overweight. Today from 25% to 40% of the adult population is considered overweight to obese. A number of factors in lifestyle patterns have changed, including amount of physical activity and cost of food. A typical family's food budget in the early years of this century took as much as 40% of the take-home dollar. Today the average family probably spends no more than 15%–20% of its earned dollars on food, and a third of that usually goes to restaurants or fast-food establishments. Food is more available now because of sophisticated growing, shipping, and storing methods. People entertain with food, conduct business over food, and generally interact socially much more around food; food is the universal bridge for social interactions.

Definitions. The National Health and Nutrition Examination Surveys (NHANES I, 1971–1974 and NHANES II, 1976–1980) measured height, weight, and triceps and subscapular thickness to define "overweight," "severe overweight," "obesity," and "severe obesity" (2). For men, "overweight" was defined as a body mass index (BMI)—weight in kilograms divided by height in meters squared—equal to or exceeding 27.8 (equal to or greater than the 85th percentile of 20-to-29-year-old men), and "severe overweight" as a BMI equal to or exceeding 31.1 (equal to or greater than the 95th percentile). For women the indices are 27.3 and 32.3, respectively.

Although the terms "overweight" and "obesity" are often used interchangeably, overweight occurs when adults exceed their desirable weight by 20% (3). The most recent indicator has been the midpoint of the recommended weight range at a specified height (medium build) as published by the Metropolitan Life Insurance Co. (4). On the average this midpoint corresponds to a BMI of 22.7; 20% above this is 27.2. "Severe overweight" corresponds to a BMI of 31.1 or greater, and would be 40% or more above the 22.7 acceptable midpoint. Again, obesity can be simply defined as referring to "fatness" or excess adipose tissue. Although fatness can be inferred from overweight, it is possible to be overweight without being obese, for example the large, muscular, well-conditioned football player.

Diabetes and Weight. Clinical observations have long suggested a connection of obesity with a variety of illnesses as well as an enormous psychological burden. The NHANES study showed a

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correlation with hypercholesterolemia, hypertriglyceridemia, hypertension, coronary artery disease, cancer, and diabetes. It has been shown that overweight Americans aged 20–75 years are at risk of diabetes 2.9 times more than nonoverweight Americans in the same age range; that overweight Americans aged 20–45 years are at risk of diabetes 3.8 times more than nonoverweight Americans in the same age range; that overweight Americans aged 45–75 years are at relative risk of noninsulin-dependent diabetes 2.1 times that of nonoverweight persons in the same age group (5).

In 1983 and 1984, Hartz et al (6, 7) studied the relationship of obesity to diabetes in regard to body fat distribution. It was their conclusion that upper body fat predominance in obesity was strongly correlated with diabetes, and the prevalence of diabetes increases with increasing values of the ratio of waist-to-hip girth. Vague (8) first noted that women with upper body fat predominance had a higher incidence of oral glucose tolerance results falling within the diabetic range than equally obese women with lower body fat predominance—"apple" or android (abdominal) versus "pear" or gynoid (hip and thigh) obesity. A more recent study by Ohlson, Larsson, et al (9) of 766 nondiabetic men followed for 13.5 years demonstrated the value of waist-to-hip ratio at baseline as a predictor for the development of noninsulin-dependent diabetes mellitus. The hypothesis is that abdominal and femoral adipocytes differ metabolically and, thus, respond differently to insulin and norepinephrine. In 1985, Leibel and Hirsch (10) summarized a study of beta 1 and alpha 2 receptors that predominate in the plasma membranes of human adipocytes. The catecholamines play a large role in the systemic energy balance determining the net quantity of lipids stored in the adipose tissue. Beta 1 stimulates lipolysis, alpha 2 inhibits lipolysis. The amount of lipids stored within any given adipocyte may reflect the net influence of these two receptors. Abdominal adipocytes are larger than femoral adipocytes and the size is related to its metabolic properties. Larger fat cells have a greater glucose uptake, but a smaller percentage increase in glucose uptake with the addition of insulin (11).

Multifaceted Obesity Control

The control of obesity, particularly obesity in the diabetic, is a major medical challenge and has been the objective of many modalities of therapy over the past years.

Multifaceted Approach. Since 1981, we at Cedars-Sinai Medical Center have been involved with the multifaceted approach to the control of obesity and obesity in the diabetic. We have used very-low-calorie diets in the form of powdered supplement, supported by a mandatory behavior modification program and encouragement of exercise. When the patient reaches within approximately 10 pounds of his or her desired goal weight, we then begin the refeeding program, along with the support of behavior modification, nutritional counseling, and prepackaged foods for maintenance. These foods are portion sized and calorie counted with sodium and cholesterol content listed. Encouraged by rapid weight reduction and better control of diabetes within a relatively short time, the patient has a greater tendency to continue with the program, particularly when they notice the accompanying decrease in the use of insulin and/or the cessation of the use of oral hypoglycemic agents.

Insulin and Weight. In our experience, exogenous insulin retards the degree of weight loss in obese type 2 diabetic patients independent of calorie intake (12). In other words, although these patients did lose weight, this group of patients who continued on their insulin had a lesser weight loss than either diabetic patients who had stopped insulin or their oral hypoglycemic agents or nondiabetics. In obese type 2 diabetic patients, weight reduction over a long period of time will result in a significant decrease in fasting plasma glucose concentrations. Improved glucose tolerance both enhances tissue sensitivity to insulin and improves insulin secretion.

Changing Learned Behavior. Overeating and obesity are the results of learned behaviors. The result of learned overeating and reduced physical activity is not necessarily a genetic or biochemical problem. In general, weight control programs have not had a favorable track record because of poor associative support systems accompanying the weight loss effort. In a study by Wing and Epstein (13) in 1985, three groups of diabetic obese patients were randomly assigned to a behavior-modification, nutrition-education, or standard-care group for an initial 16-week treatment. The behavior-modification group lost more weight than either of the other two groups during the initial four months, but at 16-month follow-up, weight losses of the behavior-modification patients were poorly maintained, so that at the end of the 16-month study there were no differences in the weight loss among the three groups. Some of the possible explanations noted were (a) the diabetic population (older and sicker—more difficult to change behavior); (b) previous history of unsuccessful weight loss; (c) program not suitable for diabetics, that is, need to focus more on health benefits such as the relationship of exercise and dieting for better blood sugar control.

Behavior or change-in-lifestyle programs strive to teach the obese person to develop a system of strategies and procedures for balancing total caloric intake and output. In other words, there are no failures except the failure of not learning how to balance caloric needs over a reasonable period of time. *Permanent weight control is impossible without some changes in the patient's basic eating and exercise behaviors.*

Very-Low-Calorie Diets. Standard hypocaloric diets have long been the basis for any weight reduction program. Fat stores are mobilized, generating ketone bodies which act as energy sources in place of glucose. This relieves the gluconeogenic burden of the liver and spares muscle breakdown to provide amino acids for this pathway. However, as a result of sustained and large caloric deficit, there will still be a mild-to-moderate negative nitrogen balance until the "balance" is restored. The very-low-calorie diets which are medically and nutritionally sound preserve the anorexic effects of fasting in the major portion of the energy deficit while decreasing the attendant ketosis, hyperuricemia, and negative nitrogen balance. The improper uses of very-low-calorie liquid protein diets (poor-quality protein such as collagen and inadequate supplemental nutrients) in the past brought notoriety to the very-low-calorie diet. One of these, the Last Chance diet (14), was used by approximately 600,000 people; 60 confirmed deaths occurred with this and similar diets (15–17). These diets markedly lacked nutritional substances, offered only poor and improper medical supervision, and use of the product was generally unstructured.

The most efficacious of the supplements in preserving lean body mass nationwide appear to be HMR-500 (Health Management Resources) and Optifast-70 (Sandoz Nutrition), and these are among the leading very-low-calorie diets used at major institutions (Table).

Protein-Carbohydrate Mixes. Drs. Victor Vertes and Sol Genuth (18–20) were the pioneers of the high-protein, low-carbohydrate Optifast program started at Mount Sinai Hospital in Cleveland, Ohio. Dr. George Blackburn et al (21) in Boston were also advocating the use of high-protein, low-carbohydrate diets for the medically obese in the early 1970s. Recent studies by Garlick et al (22) and Bogardus et al (23) using higher carbohydrate content demonstrated that blood and urinary parameters of lean body mass losses were lessened. Thus, lean body mass loss is further decreased with the higher content of carbohydrate present, along with the highest biological protein source.

TABLE

Commercial Very-Low-Calorie Diets Most Effective in Preserving Lean Body Mass

	Optifast 70	Medifast	Nutrimed	HMR 500
Nutrient*				
Protein, gm	70	45	45	55
Carbohydrates, gm	30	30	30	79
Fat, gm	2	2	0	1
Sodium, mg	920	920	920	780
Potassium, mg	1955	1000	860	2206
Calcium, mg	1000	600	600	1650
Phosphorus, mg	550	350	350	1256
Magnesium, mg	400	150	150	400
Zinc, mg	15	15	15	225
Biotin, mg	360	—	300	450
Iron, mg	18	18	18	27
Chromium, mcg	150	—	—	150
Vitamin C, IU	90	—	60	90
Vitamin A, IU	5000	—	5000	7500
Vitamin E, IU	30	—	30	45
Vitamin D, IU	400	—	400	600
Folic acid, mcg	400	—	400	450
Thiamine (B_1) mg	2.25	—	1.5	2.25
Riboflavin (B_2) mg	2.60	—	1.7	2.25
Niacin, mg	20	—	20	30
Vitamin B_6, mg	3	—	2	3
Vitamin B_{12}, mcg	6	—	6	9
Pantothenic acid, mg	10	—	10	15
Iodine, mcg	150	—	—	150
Selenium, mcg	150	—	—	150
Calories*				
(5 packets/day)	420	320	300	520

* Values obtained from manufacturer's labels.

Diets for the obese diabetic range from total starvation to varied combinations of foods, including very-low-calorie to medium-calorie diets, the American Diabetes Association (ADA) Exchange System, glycemic index programs, and the high-fiber complex carbohydrate diets of Dr. James Anderson at the University of Kentucky.

ADA Exchange System. The exchange system (ADA) is the most widely used substitution system. It consists of six exchange lists (milk, vegetables, fruit, bread, meat, and fat). Each persons's daily caloric requirement is based on ideal weight: 15 calories per pound to maintain it, 10 calories per pound to achieve it if obese, and 20 calories per pound if extremely active. Usually the protein is the component to be determined first; it is about 15%–20% of caloric needs. The fat is approximately 25%–30%, divided as follows: approximately one-third saturated, one-third polyunsaturated, and one-third monounsaturated. Cholesterol intake should be 250–300 mg per day. The remaining carbohydrate (mostly complex carbohydrate foods such as the pastas, cereals, grains, and vegetables) is approximately 55%. The division of food for noninsulin diabetics should be three food encounters per day; the insulin dependent may require 4–5 food encounters per day; depending on the type of insulin used.

Glycemic Index. The concept of glycemic index (the area under the blood glucose response for each food expressed as a percentage of the area after taking the same amount of carbohydrate as glucose [100%]) is useful for nonobese patients who don't have to pay strict attention to total calorie intake. However, studies of the glycemic effects of carbohydrates have shown that the glycemic impact of carbohydrate in complex food mixed into meals or cooked bears little relation to the glycemic values obtained when carbohydrate is ingested alone (24).

High-Fiber Complex Carbohydrates. The high-fiber complex carbohydrate diets supported by Dr. Anderson have been found to be very successful in those people who can comply with this type of diet. In his *Nutrition Management of Metabolic Conditions* (25), Dr. Anderson states that high-fiber foods promote weight loss for a number of reasons. Eating fiber-enriched foods may take longer, contributing to satisfaction and satiety. Soluble fiber slows gastric emptying, contributing to a feeling of fullness. Serum insulin concentrations are lower after high-fiber meals. Starches are less easily digested and absorbed from whole wheat bread than from white bread, and more energy may be expended in digesting and absorbing high-fiber than low-fiber foods. But even Dr. Anderson agrees that high-fiber diets are not for everyone. Generally, older persons have greater difficulty modifying their eating habits. People who live alone, cook little, or eat most of their meals away from home have difficulty in adhering to a high-fiber diet. The experience of bloating and flatulence may turn a lot of these patients away from the high-fiber diet.

Sweeteners. An important aspect of dietary control in the diabetic patient is the proper use of sweeteners. Table sugar (sucrose) raises blood sugar quickly. Similar "rapid responders" which are rapidly converted into glucose are honey, molasses, maple sugar, dextrose, corn syrup, and milk chocolate. These add calories and make blood sugar difficult to control. The nutritive sweeteners include fructose, sorbitol, and mannitol. Fructose is found in honey and fruits. It is absorbed more slowly; however, when diabetes is uncontrolled, fructose will be quickly converted into glucose by the liver. Consumption of fructose should not exceed 75 gm/day.

Sorbitol is about half to two-thirds as sweet as sucrose. When used in quantities of 50–80 gm/day it may cause gastrointestinal distress and diarrhea. Mannitol is about two-thirds as sweet as sucrose and when used in quantities of 20 gm or more may produce diarrhea.

The "artificial sweeteners" do not add significant calories to the diet, but have their own inherent problems. Cyclamate was first synthesized in 1939 and used extensively from 1950 to 1969. It is 30 times as sweet as sucrose. Cyclamate was banned in the United States in 1969 when evidence was introduced that very large amounts given to laboratory animals produced cancer; however, no such evidence was ever noted in humans. Today it is still used widely by many other countries.

Saccharin was introduced in 1979. It is 200–300 times sweeter than sucrose. Its main disadvantage is a metallic aftertaste. Although questions have been raised about its safety, no substantial evidence has been found to warrant its removal from the market.

Aspartame was discovered in 1965 and approved by the FDA in 1981 for dry products and in 1983 for soft drinks. It is 180–200 times sweeter than sucrose. In the form of Equal (Searle), it contains some dextrose and dried corn syrup and therefore has 4 calories in each packet. Its main disadvantage is that it becomes unstable when heated and therefore cannot be used in cooking. Aspartame breaks down into aspartic acid, phenylalanine, and methyl alcohol (methanol). The only warning given is that people with phenylketonuria may exhibit central nervous system manifestations with large amounts of aspartame.

The ADA recommends limiting aspartame to 50 mg/kg/day. Combinations of sweeteners are being tried, since the results are synergestic and help counter the disadvantages of the individual ingredients (26).

Exercise. Physical exercise has always been recommended as an important part of any weight-control treatment for the obese. Exercise is a physiologic state requiring the rapid mobilization and redistribution of metabolic fuels to ensure an adequate energy supply for the work of muscle contraction (27). Muscle glycogen serves as a source of energy in the first few minutes of exercise because it is directly available to tissue; however, it is only a limited energy source. The main oxidative fuels that contract muscle are glucose and free fatty acids. At the onset of exercise carbohydrate becomes the more important oxidative fuel. Hormonal responses to exercise include decrease in insulin secretion and increase in the circulating concentration of catecholamines, glucagon, growth hormone, and cortisol. The decrease in insulin secretion facilitates production of hepatic glucose and mobilization of free fatty acids from adipose tissue. Thus, insulin plays a central role in mediating these metabolic pathways. A significant decrease in plasma glucose occurs in response to 45 minutes of moderate exercise. Exercise provides a sense of psychological well-being, increases energy expenditure, suppresses appetite, brings changes in circulating lipoproteins, increases maximum oxygen uptake, lowers blood pressure, and decreases coronary artery disease. Evidence of a significant beneficial effect of exercise on glucoregulation has not been clearly demonstrated, however. Since the long-term effect in improving blood glucose control is measured by glycosylated hemoglobin, the response to exercise has not been evident by itself (28–32).

It is evident from the preceding discussion that no single modality or entity can sustain the reduction of obesity, in the diabetic as in others, and make him/her normal glycemic. Only a combination of good diet, health-promoting behavior, and a good medically supervised program, followed daily, weekly, and for the rest of the individual's life, can maintain weight loss and good health.

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Current Status of Insulin Pumps

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Insulin pump therapy is currently viewed as a viable alternative to conventional insulin injections in the treatment of insulin-requiring diabetes mellitus (1–3). It may be considered an option for patients willing to participate in an intensive insulin therapy regimen in which they utilize results of frequent daily home blood glucose tests along with their knowledge of diabetes and diet to adjust their daily insulin doses (4).

Insulin pumps, which were modeled after the pumps used for continuous infusion of chemotherapeutic agents, became increasingly common in the treatment of diabetes in the late 1970s and early 1980s (5). It was initially thought that continuous subcutaneous insulin delivery via the pump would offer a major advantage over any other available method of insulin delivery by closely mimicking insulin secretion from a normally functioning pancreas. However, the potential for mechanical breakdown and operator error, as well as the increased need of professional time and knowledge, have prevented a more widespread use of insulin pumps; these factors highlight the importance of careful selection and intensive education of patients before initiating pump therapy (6).

Most insulin pumps consist of a 1–3cc syringe connected to a 21–42-in thin tube with a needle attached. Regular (short-acting) insulin is used to fill the syringe and tubing and a new needle is inserted subcutaneously (preferably in the abdomen) every 2–3 days. Insulin is delivered in two ways: a continuous low basal infusion (typically 0.5–1.5 units/hr), and bolus doses before meals and snacks.

Current Equipment. As many as 15 different insulin pumps have been on the market; 6 to 8 are currently available. During the last five years, pumps have undergone tremendous technologic advances. The trend is toward smaller, more sophisticated pumps with internal clocks, multiple alarms, and automatic multiple basal rates. An important element in the successful use of the insulin pump is to match patients' priorities for pump characteristics with the unique features of each pump (see box).

During the last five years improvements have been made in the quality of usable items such as syringes, tubing, and needles, leading to fewer pump-related difficulties (tubing leaks or clogs) and increased patient comfort (easier needle insertion).

It is sometimes assumed that the more sophisticated and complex the pump, the better the chance of achieving good diabetic control. That has not been our experience at Cedars-Sinai Medical Center, where patients are offered pumps with a variety of different features and where patients have been able to achieve normal glycosylated hemoglobin values with the simplest of insulin pumps (7).

The two main advantages of insulin pump therapy are that it offers the potential for achieving euglycemia and, in addition, more freedom and flexibility in the lives of pump users.

Potential for Euglycemia. For most patients, the pump itself does not necessarily lead to euglycemia. It is other factors—such as intensive diabetes education, increased enthusiasm for monitoring blood sugars and diet intake, and frequent contact with health professionals—that positively influence glycemic control (8). There is no consensus in the literature on the comparative value of insulin pumps versus multiple daily injections for glycemic control. Crossover studies have reported either better control by insulin pumps (9–11) or no difference in control (12–14) when comparing the two. In our experience fasting glucose levels have been a decisive factor.

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Features of Currently Available Insulin Pumps*

Size: weight, 3–8 oz; average dimensions the size of a deck of cards

Cost: $900–$3,300 per pump; some pumps available for monthly rental

Power: rechargeable battery packs changed every 1–3 days or nonrechargeable batteries lasting from 3 weeks to one year, depending on the pump and the total daily dosage delivered

Complexity: 1–4 different automatic basal rates; various alarms (low or dead battery, occlusion, operator entry error); computerized (digital-like) operation or simple manual bolus administration

Company characteristics: length of time on market, provision of ancillary services (loaner pumps, education programs, literature, 24-hour troubleshooting assistance)

* For a detailed description of insulin pumps currently available on the market, see *Diabetes Forecast*, Jan/Feb 1986.

That is, if this value is easily controlled by multiple insulin injections, pump therapy provides a similar level of control, whereas for a small number of patients with fasting glucose concentrations difficult to regulate satisfactorily on multiple injections, pump therapy has improved the fasting glucose levels. Additionally, a small group of patients who have benefitted from insulin pumps are those who are truly brittle with wide swings in glucose level despite all efforts by the patient and the professionals caring for them; for these patients, receiving varying basal rates with no or very small boluses of insulin from a pump often leads to fewer wide swings in blood sugar and sometimes to overall better diabetic control.

Flexibility in Daily Life. For most patients, the freedom and flexibility in daily schedule that is possible with the pump (independent of the level of diabetic control achieved) is its major advantage. Insulin pumps offer a greater potential for varying meal times and content (15, 16) and for skipping meals. Unlike intermediate- or long-acting insulin, the basal rate can maintain glycemic control in the absence of food, and bolus doses are taken only when food is to be eaten. Additionally, some patients find their lifestyles enhanced by the greater ease and speed of insulin dose delivery by the pump compared to multiple injections.

Disadvantages. The disadvantages of insulin pump therapy reported in the literature may or may not be pump-specific problems. For example, problems such as increased occurrences of hypoglycemia are frequently related to the lowered target ranges of any intensive insulin therapy regimen (14), and occurrences of diabetic ketoacidosis are frequently related to inappropriate patient responses to illness (17). Patients experiencing these problems on the pump are likely to experience them with another intensive insulin regimen.

The occurrence of hypoglycemia or hyperglycemia may, however, be pump-related, as are infections at the sites of needle placement. Hypoglycemia may be the result of an operator error in dose administration with the pump or the result of "pump runaway" (a very rare occurrence involving nonprogrammed insulin delivery by the pump). Hyperglycemia may be related to loss of integrity of the delivery system, including a needle or tubing clog or tubing leak, or it may result from an operator error such as running out of insulin or not responding to an alarm in a timely fashion.

Many of these problems are preventable, or at least detectable and correctable, before blood sugar control is seriously compromised (14). In the case of needle-site infections, more frequent needle changes with daily self-assessment of sites leads to a decrease in infections and to the prevention of serious infections should a superficial one be detected.

Choosing Candidates. The two most important factors to assure successful and safe use of the pump are daily self-monitoring of blood glucose throughout the day (at least four times if possible), which allows the patient to detect unexpected changes in glucose control, and education in troubleshooting the insulin pump before use commences.

In choosing a candidate for insulin pump therapy many characteristics are considered, including age, status of diabetic complications, motivation, education, emotional stability, financial resources, lability of diabetes, treatment goals, and patient preference. Some programs may limit pump candidacy to people with type 1 diabetes (18), to people without serious diabetic complications (4, 5), or to people who have been unsuccessful with another form of intensive insulin therapy (8). The experience of the Cedars-Sinai insulin pump program suggests that pump therapy can be appropriate in a variety of patients, provided they receive thorough training in using the insulin pump and in managing their own diabetic control. In addition, patients are shown a variety of insulin pumps so that they can choose the pump appropriate for their own needs.

Twenty-seven patients ranging in age from

13 to 69 years have begun insulin-pump therapy (using 6 different pumps) over 2½ years at Cedars-Sinai Medical Center. The pump users have had diabetes for 8 months to 15 years prior to initiation of pump therapy, and have been on injection regimens including 2 to 4 injections per day prior to pump therapy. Some have had no diabetic complications, others have had retinopathy, neuropathy, and nephropathy in varying stages. They have checked blood sugars with visual strips or meters. All but two have received 80% to 100% insurance coverage when letters of medical necessity were sent by the physicians; one of the two exceptions is on Medicare, and the other has not yet received a decision from the insurance company.

Complications that have occurred since the initiation of pump therapy have included one dropout secondary to pump breakdown with subsequent withdrawal of the pump company from the market; one hospitalization for nausea, vomiting, and dehydration secondary to mild diabetic ketoacidosis during an illness because of failure to increase insulin doses appropriately; one pump-related hypoglycemic episode treated in a hospital emergency room caused by pump infusion at 10–20 units unexpectedly (the pump was subsequently withdrawn from the market); infections at the needle insertion sites in 3 patients who were treated with oral antibiotics at home; and pump-related hyperglycemia, averaging once every 1 to 3 months per patient, secondary to tubing clogs or leaks (this has recently decreased with improved tubing on the market).

Patients in this program have shown a general trend toward improved control. All patients report improved lifestyle with more flexibility. Despite the occurrence of pump-related hyperglycemia, none of the pump users have been willing to go back to multiple-injection therapy, and three patients who rented pumps opted to purchase them after 3 to 4 months. The average glycosylated hemoglobin (normal, 4.2%–6.8%) results were 9.3% prior to initiation of pump therapy or prior to affiliation with the Cedars-Sinai pump program (for patients who joined the program while already using a pump); 7.8% 3 months later; and 7.7% 9 months to 2 years after starting in this program (N = 16). Those patients not represented in these values include one teenage patient who consistently falsified her home glucose test results; 3 patients who have not yet been using the pump for 3 months; 1 patient who has relocated; and patients who are being followed by physicians in the community after utilizing the Cedar-Sinai pump program for outpatient prepump education and inpatient initiation of pump therapy.

In our view, insulin pump therapy offers two important benefits. As one form of an intensive insulin regimen, insulin pump therapy offers an improved opportunity to achieve near euglycemia. Second, it offers a more flexible lifestyle for diabetic patients, independent of its overall effect on control. Thus, appropriate patients should be given the opportunity to seek information about insulin pumps from health care professionals experienced in this form of treatment to enable the patient to make informed decisions regarding insulin pump therapy.

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Compliance, Education, and Diabetes Control

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"Diabetes is a disease which . . . develops character, for to follow rules involves self control" (1).

It is not likely that many of our patients accept Dr. Joslin's flinty Yankee suggestion that diabetes is "good for the soul." On the contrary, I expect that most of them find it an unremittingly terrible condition. It is fatal for many, a fact that coroners and epidemiologists alike continue to often overlook (2). It is rarely cured, even though the vast majority of patients have features that theoretically could be managed well without drugs (3). Lastly, it requires almost constant, persistent attention. In fact, of all chronic diseases, diabetes seems to be foremost in putting the responsibility for ongoing good health squarely on the shoulders of the patient.

The Problem of Compliance

Assuming responsibility for one's own health is not easy. Proper diabetes treatment requires not simply that our patients take their medication and visit their doctor, but that they ultimately make true lifestyle changes (4, 5). Yet "a major and substantial change in behavior is easy to discuss but hard to achieve" (4). For one, the patient may view the treatment of diabetes as being worse than the disease itself (5). The potential for developing a long-term complication is far less real to some patients than the restrictions placed on their eating habits, the need for implementing a regular exercise schedule, or (worst of all) the indignity of taking insulin injections. Even sophisticated patients, more accepting of the fact that they are "diabetic," are often more wary of hypo- than of hyper-glycemia (despite what their physicians tell them) and are unable to adapt to the never-ending regimen of daily self-glucose monitoring and multiple insulin injections.

Each of the many adjustments we expect diabetic patients to make to get optimal sugar control has been considered near-impossible to achieve in other groups of patients. Weight loss and maintenance of long-term weight control is an elusive goal for the vast majority of obese patients, despite special diets, complicated medical or surgical regimens, and multiphasic programs (6). Dietary change, the cornerstone of diabetic therapy, is difficult for all but the most dedicated patients, not surprisingly considering the years of patterning that go into individual diet selections (7). Finally, even in our fitness-oriented society, it is extremely difficult to motivate sedentary patients to begin and maintain an exercise program, even with the threat of osteoporosis, heart disease, and other medical complications (8).

In the past decade, diabetes care has changed dramatically. Yet the truth is that each of these modern developments has brought new responsibilities to the diabetic patient. Most patients and physicians, it is to be hoped, are now aware of the inadequacy of urine testing for most clinical decisions and the need for blood glucose monitoring. Up-to-date diabetic patients must learn the intricacies of self-monitoring of blood glucose and methods for recording and analyzing the data. They discover that in clinical care, "You get what you pay for," and that even a reduction in monitoring from four to two times a day may be associated with a significant worsening in blood sugar control (9). Finally, many patients with

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Type 1 diabetes discover that the need for intensive monitoring and careful attention to detail does not wane with the passage of time. For most of them, monitoring does not yield an immutable "answer" that fixes their insulin needs, but only a relative "process" that allows them to follow their changing requirements and develop a flexible approach to glucose control. Small wonder, then, that patients are often overwhelmed by the personal responsibility inherent in optimal diabetes care (10). One patient of mine told me that she had to do 22 specific "things" a day in order to follow her diabetes schedule and that she didn't quite feel up to doing it every day of her life!

The inability of patients to do exactly what we want is so rampant (and so disturbing to physicians) that we've made it a diagnosis: "noncompliance" (4, 5). Inherent in this term is the rather iatrocentric concept that if only "they" could get over their problems, "we" could get on with treating their disease. Yet real solutions to this problem can come about only through understanding the need for restructuring the classical doctor-patient relationship and bringing the diabetic patient more into the health assessment and goal setting process. As Anderson has pointed out (5), the doctor may be an expert in diabetes, but the patient is an expert about his or her own life.

Incorporating the patient more into the health care process is difficult, requiring such steps as renegotiation, education, motivation, and communication (5). The educative process, stressed here, is primary, since in order to work together, patients and physicians need a common understanding of the rationale of diabetes care: the basics of diabetes, the importance of control in preventing complications, and the role the patient has to play in day-to-day diabetes management (11).

Patient Education

Defining the Need. Patient education in diabetes care is not new (12), although acceptance of it in the general medical community is. The need for improving patient knowledge should be obvious to anyone who works with diabetic patients, and published studies reinforce the impression that most patients with diabetes know relatively little about their disease (13–15). For example, in Miller's study (13) at a county hospital of patients who had attended diabetes education programs, 45% of the patients evaluated could not demonstrate adequate knowledge in *any* of the identified major areas of self care. Private patients don't seem to do materially better (15), and it is not completely clear what determinants do help establish effective knowledge (16), although age (14), duration of diabetes (17), and socioeconomic status (14, 17) have all been proposed as being important.

Diabetes education for patients comes in all shapes and sizes. Traditionally, patient education has been considered a responsibility of the hospital (18) and, in fact, in the last decade the Centers for Disease Control found that the vast majority of hospitals in most states offered inpatient education services (19). For a disease like diabetes, of course, the wisdom of extensive inpatient education has to be questioned, considering the need for adapting the lessons of proper treatment to the patient's own environment. Still, before the 1980s it was difficult to find much in the way of *outpatient* educational facilities for diabetes. In 1978, for example, a study in Maine showed that all acute care hospitals surveyed had inpatient education programs (however meager), although less than 6% had formalized outpatient services (19). Similar findings were noted in other states, as in Ohio, where 28% of 207 hospitals provided no individual outpatient diabetes education at all, and in Rhode Island, where only 2 of 15 hospitals had outpatient programs. In the latter state, only 31% of hospitalized diabetic patients less than 30 years old reported ever having received two or more hours of outpatient education, even though they had had diabetes for a mean duration of 10 years (20)!

Even within the outpatient setting, a variety of approaches has been used to educate patients with diabetes, ranging from one-on-one sessions, to groups, to extensive training courses (21). At Cedars-Sinai Medical Center in Los Angeles, inpatient education had long been supported with outpatient follow-up sessions, usually one-to-one. Outpatient group classes had been offered irregularly, usually when there was a perceived need for information about a specific topic, such as pregnancy or exercise. However, although considerable effort had been made to obtain insurance reimbursability for diabetes education services (22) and to promote these services to the local medical community, the utilization of the one-on-one program was disappointingly low, and there was little to suggest that we were making an important impact on patients' long-term health. Thus, in April, 1984, the Diabetes Outpatient Training and Education Center (DOTEC) was opened in an attempt to expand the existing education services and to qualitatively change the effect we might have on patients' own diabetic control.

Patient Self-Management: Diabetes Outpatient Training and Education Center. The Diabetes Outpatient Training and Education Center (DOTEC) program at Cedars-Sinai is a five-day, intensive training program for diabetic patients and their families. Models for such a program exist in Minnesota (12), Washington state (23), New York (21), and other states, all of them sharing the common goal of patient self-management of diabetes. Like these other programs, DOTEC is an outpatient facility; patients come from home (or neighboring hotels) five days in a row, Monday through Friday, generally from 7:30 AM to 3:30 PM. To minimize patient fatigue, the DOTEC educational syllabus is presented in a variety of styles and settings (Table). Throughout their week, therefore, patients participate in didactic lectures, small discussion groups, and one-on-one sessions; the faculty is rotated as often as possible. Diabetes teaching nurses and specially trained dietitians do the bulk of the DOTEC teaching, but genetic counselors, exercise therapists, psychologists, and physicians are also used to highlight specific aspects of the syllabus. (For some of the patients, particularly those who have been through training programs in the past, it is the presence of these "special" lectures that attract them to the DOTEC program in the first place, even though our staff usually feels that they are just as much in need of learning the basics of diabetes as are the other patients.)

The Physician at DOTEC. The physician at DOTEC plays a number of different roles. Unlike many other diabetes education programs around the country, the DOTEC program has been set up with the aim of being a service to local physicians by offering their patients resources that cannot be provided in the average office. Thus, as we guide the patients to take a more aggressive role in their own medical care, we try to maintain close contact with their primary physician. Good communication is essential to avoid any conflicts over long-term treatment goals and to maintain our proper role in this medical community.

During the week, patients are seen every morning by the program physician, the teaching nurse, and the dietitian, and the entire team (including the patient, of course) reviews the results of the glucose monitoring done on the previous day. Minor changes in therapy suggested by the data are implemented at that time. However, not infrequently, patients take the program lectures to heart and decide to make major alterations in their treatment schedule, often desiring a multiple insulin injection regimen. At this point, the patient's private physician is called to discuss the implications of such an important change in therapy. Usually, the physician is happy to support a more aggressive treatment schedule.

In addition to contacting the patient's physician during the week if necessary, at the end of the training program, the patient's doctor is again called to "tie up loose ends" and a week or so later we send a follow-up report with the patient's glycosylated hemoglobin value. Furthermore, although patients are urged to follow-up with the program nurse and dietitian after the completion of the program, they are not permitted to follow-up with the program physician. As rigid as this seems, it is clearly the only way to avoid the enmity of the local private physicians, a necessity with such a hospital-based program as ours.

The physician is also an educator in this program. For example, the lecture that starts the week, "The Case for Control," serves as a crucial starting point for the teaching program, outlining for patients the medical rationale for participating in the first place: to be able to control their blood sugars in as normal a fashion as possible, in order to avoid chronic diabetic complications.

At the next lecture by a physician, on Day 2, patients are taught not just why, but how to use insulin in a maximally effective manner. For many patients, the only thing important to them about using insulin is whether or not they have to. They've given little thought to the intricacies of using it properly and have never really considered the pharmacologic options open to them. The content of this lecture is almost identical to that given to the residents and interns rotating through our diabetes service or to community physicians in continuing medical education. (We have had few problems with patients understanding these "medical" concepts of insulin use. In fact, most of them express great interest in analyzing how insulin actually works in their own bodies, instead of relying on what's "supposed" to happen.) In this lecture, the different strategies used to treat diabetes are discussed ("simplest is best" vs. "flexible control") and the time courses of available exogenous insulins detailed and contrasted to the physiologic curve of normal insulin secretion. Changes in therapy are not directly suggested at this point, but patients are encouraged to use glucose monitoring to find out where their own insulin fails to work adequately. They

TABLE
DOTEC Class Schedule

Topic	Setting	Educator
Monday		
Tour & introduction	Entire Facility	Staff
What is DM and the case for control	Lecture Room	Physician
Hypoglycemia	Lecture Room	Nurse
General diet principles	Lecture Room	Dietitian
Introduction to psychological aspects of diabetes	Breakfast Room	Psychologist
Evaluation of control	Patient Lab	Nurse
Tuesday		
Daily Assessment	Patient Lab & Breakfast Room	Staff
Insulin	Lecture Room	Nurse
Management of Blood Sugar Patterns	Lecture Room	Physician
Behavior Modification	Lecture Room	Dietitian
Glycosylated Hemoglobin	Patient Lab	Nurse
Exercise and Diabetes	Exercise Yard	Exercise Physiologist
Wednesday		
Daily Assessment	Patient Lab & Breakfast Room	Staff
Oral Hypoglycemic Agents	Lecture Room	Nurse
Restaurants & Alcohol	Lecture Room	Dietitian
Travel & Sick Day Rules	Lecture Room	Nurse and Dietitian
Faculty Open Forum	Breakfast Room	Staff
Food Labels & Sweeteners	Lecture Room	Dietitian
Long-term Problems	Lecture Room	Physician
Thursday		
Daily Assessment	Patient Lab & Breakfast Room	Staff
Equipment Review	Patient Lab	Nurse and Dietitian
"Speak Out" Group Discussion	Lecture Room	Psychologist
Fiber & Glycemic Index	Lecture Room	Dietitian
Genetics of Diabetes	Lecture Room	Genetic Counselor
Friday		
Daily Assessment	Patient Lab & Breakfast Room	Staff
Cooking Principles	Breakfast Room	Dietitian
Insulin Pumps	Lecture Room	Pump Nurse
Care of the Feet	Breakfast Room	Nurse
Research in Diabetes	Lecture Room	Physician

often express the opinion that they had never before thought of tailoring the insulin to meet their own needs; rather, they had always changed their schedules to meet the demands imposed by their insulin.

In the latter half of the DOTEC week, patients are given a lecture by a physician on diabetic complications. This topic is obviously fraught with emotional content, and some patients have cried, others have even left during the lecture. Nonetheless, it is clear that "the devil you know is better than the devil you don't know," and that patients want to know what is likely to happen, what may happen, and what will probably not happen to them. They overwhelmingly approve of this detailed review of complications, and often bring family members to sit in on this specific lecture.

The last lecture of the week is also by a physician. A review of research in diabetes, it is designed to end the week on an upbeat, giving patients with both short-term and long-term diabetes a hope for future developments that can help them in their lifelong treatment. We focus in this lecture on three aspects of clinical research: (a) prevention of diabetes (all diabetics are concerned about family risks), (b) inventive treatment of blood sugar (from nasal insulin to pancreatic transplants), and (c) prevention or stabilization of complications (emphasizing the hope for those who in the past have been, or may in the future be truly unable to attain physiologic blood sugar control). The week thus concludes with an unstated contract: that we in the diabetes community, while working with patients to obtain the best control they can, will continue the search for a "cure." For their part, our patients agree to continue their day-to-day control, in part so they'll be as healthy as possible when the next research breakthrough comes along.

Does Patient Education Really Make a Difference?

The burgeoning literature on diabetes education (24) and the publication of policy statements from national organizations (25) both speak to the growing interest in patient education in the diabetes community. However, almost as soon as these signs of support appeared, questions were raised, appropriately, about the evidence that education does, in fact, improve the care of the patient with diabetes (26, 27). Evaluating that hypothesis first requires that we define the parameters by which we will judge "improvement." "Preventing complications" or "extending lifespan" seem worthy but are distressingly distant criteria. On the other hand, "more diabetes knowledge" may turn out to be necessary but is unlikely to be a sufficiently powerful criterion. I believe there are four separate aspects of patient care and competency that are important in evaluating the efficacy of educational programs:

Patient Knowledge. A number of investigators have developed tools for testing and following patient understanding of diabetes and its care (16, 28–31). In most studies, both pediatric (29) and adult patients were able to demonstrate an improvement in cognitive knowledge about many aspects of diabetes after education sessions lasting from a few hours (29, 30) to a number of days (31). Unfortunately, this improvement in knowledge was usually demonstrated shortly after the completion of the program itself; long-term follow-up has often shown this increase in information to be evanescent (32–34), even after as short a time as one month. Furthermore, many studies fail to show a correlation between improvement in knowledge and improvement in other parameters of diabetes care (see below) (29, 32, 35), one even demonstrating that significant clinical benefit could be seen 18 months after an education program, even though patients didn't know any more than a control group receiving minimal education (36). Despite this last finding, I think an increase in diabetes knowledge is likely to be relevant to the process of improved control, even though there may not be a direct link.

Patient Behavior. Clearly, if we wish to ultimately improve patients' health, what they do is likely to be more important than what they know. With this in mind, many programs have taken a "behavioral" approach to education, with an emphasis on self-care practices (26). Nonetheless, studies on behavioral outcomes have reflected the same problems as outlined above for the "knowledge" criterion: improvement in patient management skills is often evanescent (34), and change in patient behavior does not always correlate with change in diabetes control (35, 37). Still, an imaginative dietary education program was able to change what patients actually did (as well as knew), and this improvement in dietary practice (greater stability of carbohydrate intake) correlated with an improvement in glycosylated hemoglobin values (30). Other studies have also shown persistent changes in "good behavior" after some education programs (35, 36) and with confirmation of our clinical impression that self-taught patients do not "perform" as well as those trained by diabetes professionals (38), there seems to be good reason for continuing to teach proper patient skills in diabetes management.

Patient Attitude. Diabetes management requires not only that patients do a stated number of explicit tasks, but that they truly integrate the care of diabetes into their own lifestyle. This need for "living" with diabetes day after day takes its own toll on patients' health, and improved care can be judged in part by the ease with which patients adapt to the emotional demands of diabetes (29). Few programs try to influence patients' emotional status directly, yet a recent study showed that long-term improvement in diabetes control correlated not with participation in the intensive education program being evaluated, but with a low score (at the intake evaluation) for anxiety and depression and a high score for self-confidence (39). Other studies have demonstrated similar findings (40, 41). This seems particularly significant in light of a report that patients with type 2 diabetes showed a reduction in anxiety scores after participating in a diabetes education program (42) (and that anxiety scores went up if they were put off a month before being enrolled). Other studies have shown that education can lead to an improvement in a positive "attitude" toward diabetes, one that persisted for at least three months after the program (31).

Patient Control of Blood Sugar. This is the one criterion that everyone would accept as being important, and in many respects is the one most difficult to prove. The published data are decidedly mixed. As noted above, many studies have shown improvement in knowledge or behavioral skills, without a concomitant improvement in diabetes control (29, 35). A few uncontrolled studies have shown glycemic improvement (21, 31), some persisting as long as two years after training (43, 44), although causal relationships are difficult to demonstrate, particularly when the patient education has been integrated into an ongoing treatment program (43, 44). Although uncontrolled, Jovanovich's study (21) is especially interesting, for in comparing a number of different types of education programs offered at her institution, she concluded that long-term improvement in control was found only when a program met three criteria: the staff utilized a team approach, education was done in a group setting, and at least 35 hours of education were offered (similar to what is done at DOTEC at Cedars-Sinai).

A well-designed study requires both a properly selected control group and the ability to isolate the effect of education from other aspects of intensive diabetes care. A number of controlled studies have failed to demonstrate any distinct effect of education (23, 39), although criticism has been raised of one program (39) that the educational syllabus was inadequate (45, 46). A controlled study of patients with type 2 diabetes referred to an education program (with entry of half the patients deferred) showed that indices of glycemic control improved after participation in the program (42). However, as so often seen, these effects were not sustained past the second month. A most recent report of a controlled study is the most impressive. In this report, 275 patients were followed through a number of randomized educational options (36). The patients' self-care skills, compliance behaviors, fasting blood glucose values, and glycosylated hemoglobin values all improved as a result of intensive education, and these improvements were maintained 11–14 months following instruction.

The true role of patient education in the treatment of diabetes has yet to be defined. Cautious voices have been raised, suggesting that the total cost of education programs has rarely been confronted and that we are a long way from extrapolating the results seen in a small number of patients to diabetic patients in general (27). On the other hand, the National Diabetes Advisory Board has started a process designed to develop standards for education programs in this country (25) and third-party payers have been approached to support education as an important tool for the treatment of diabetes (47). The literature to date is sparse, but it suggests that hospitalizations for diabetic patients can be reduced through education (42, 48) and that glycemic control may be improved long-term (21, 31, 36, 43, 44). Although we need more confirmatory studies, it is likely that we will see an expansion of the diabetic education facilities currently available. It remains to be seen if primary care physicians and the majority of diabetic patients will take advantage of these opportunities.

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Natural Course and Management of Diabetic Retinopathy

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Diabetic retinopathy is one of the leading causes of blindness in the United States today (1, 2). An estimated 10 million people have diabetes mellitus in the United States, and about 40% of them develop some form of diabetic retinopathy (3, 4). Of these, 90% have nonproliferative retinopathy and the remaining 10% develop proliferative retinopathy (5).

The duration of the disease and the age of the patient are both important factors in the development of diabetic retinopathy. The longer the course of the disease, the more likely is a patient to develop some form of retinopathy (6–8); after 20 years of the disease, the likelihood is 75% to 80% (9). Evidence of retinopathy in the newly diagnosed juvenile diabetic is unusual, but quite common in the newly diagnosed adult. Occasionally it is the ophthalmologist who makes the initial diagnosis of diabetes upon finding diabetic retinopathy.

Classification and Clinical Findings

Diabetic retinopathy is a microangiopathy of the retinal circulation, the mechanism of which is poorly understood. The retinal capillaries become incompetent and leak fluids inside the retina, leading to nonproliferative diabetic retinopathy (NPDR). As the disease progresses, thickening of the capillary walls and capillary closure occur, leading to retinal ischemia and retinal neovascularization, denoting proliferative diabetic retinopathy (PDR). As the retinopathy changes from the nonproliferative to the proliferative stage, the retina shows characteristic changes that herald the onset of PDR. This transitional phase is called preproliferative diabetic retinopathy (prePDR).

PDR is the most aggressive form of diabetic retinopathy and may lead to total blindness. It has a poorer prognosis than NPDR, which may produce visual loss of variable degree (but not total blindness), or may have no effect on the vision at all.

Nonproliferative Diabetic Retinopathy. The retinal findings of NPDR, or background retinopathy, include microaneurysms, dot and blot hemorrhages, hard exudates, and macular edema.

The retinal capillary endothelial cells and pericytes weaken, leading to microaneurysms, focal capillary sacculations, that are the first sign of diabetic retinopathy. Those are more commonly seen on the temporal aspect of the macula, but may be seen anywhere in posterior pole. They can remain stable for months, or disappear and reappear at variable intervals (10). Microaneurysms, however, are not specific lesions of diabetic retinopathy and may be seen in a wide variety of retinal vascular disorders.

Capillary decompensation leads to small focal intraretinal hemorrhages. Some occur in the inner retinal layers, producing flame-shaped hemorrhages; others occur in the depth of the retinal layers, producing dot and blot hemorrhages. As for the microaneurysms, the retinal hemorrhages can remain stable for months, or disappear and reappear at variable intervals. They can also occur in a variety of retinal vascular disorders and are not specific to diabetic retinopathy.

The retinal capillaries and microaneurysms lose their tight junctions and leak lipids and lipoproteins, leading to the formation of hard exudates. Those are sharply defined, glistening, yellowish crystals that are deposited in the middle layers of the retina. They disrupt the retinal

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structure, particularly when they lie in the macular area, causing the destruction of visual cells and resulting in visual loss.

Extravasation and collection of fluid and hard exudates into the retinal extracellular space leads to retinal edema. When the edema and the hard exudates involve the macula, the visual acuity drops according to the degree of macular involvement. Macular edema and lipid collection in the central macula are the most adverse effects of diabetic capillary disease and are largely responsible for visual loss in NPDR (5).

Preproliferative Diabetic Retinopathy. The Diabetic Retinopathy Study Research Group (DRS) reported a 50% chance of developing neovascularization in one year, in eyes with advanced prePDR (11). The recognition of this stage should alert the physician to the active changes occurring in the retina that will end with retinal neovascularization and its dreaded complications. Closer ophthalmic supervision of the patient is necessary to allow intervention when needed.

In prePDR the retinal findings are the same as in NPDR, with the addition of venous abnormalities, nerve fiber layer ischemia and infarction (cotton-wool spots), and intraretinal microvascular abnormalities (IRMAs).

Venous abnormalities are common nonspecific findings, generally related to increasing retinal ischemia. The venules assume a "sausage" beaded appearance. At a later stage, venous loops may occur.

Cotton-wool spots, or "soft exudates," are findings of important clinical significance. They are retinal nerve fiber layer infarcts that occur as a result of capillary closure and are thus the expression of retinal ischemia, which has been shown to be the precursor of retinal neovascularization (12, 13). The cotton-wool spots are pale yellow patches with poorly defined margins. They are more difficult to identify with the direct ophthalmoscope because their borders do not contrast well with the normal retina. They are better seen with indirect ophthalmoscopy, which allows a "bird's-eye" view. They tend to disappear in a few months, sometimes followed by the formation of patches of retinal neovascularization adjacent to their previous location. The cotton-wool spots are also the hallmark of the retinopathy of systemic hypertension, and these follow the same course as those of diabetic retinopathy.

Intraretinal microvascular abnormalities (IRMAs) are fine networks of retinal capillaries abnormally developed within the retinal tissue that have not yet broken the internal limiting membrane of the retina and are not yet exposed to the posterior vitreous face. They develop as a result of retinal ischemia and are commonly present in the posterior pole or the midretinal periphery. IRMAs become more visible as the retinal ischemia becomes more extensive in prePDR, but disappear as neovascularization develops.

Proliferative Diabetic Retinopathy. PDR occurs in about 10% of all diabetics; 50%–90% of them will go blind within a period of one to five years (14). The natural course of PDR includes the following events, in no set order:

neovascularization at the disc (NVD)
neovascularization elsewhere in the retina (NVE)
fibrovascular proliferation
vitreous hemorrhage
traction retinal detachment
neovascular glaucoma
total blindness

Retinal neovascularization is the hallmark of proliferative diabetic retinopathy. Whereas the intraretinal microvascular abnormalities (IRMAs) of prePDR occur within the retina itself, the new vessels break the internal limiting membrane of the retina and lie on its surface. This is an important distinction, because the membrane break starts a cycle of complications due to the adherence of the new vessels to the posterior vitreous face. The neovascularization can occur either on the optic nerve head (NVD) or anywhere else on the retina (NVE). These new vessels are incompetent and leak blood products into their immediate surroundings, particularly on the posterior vitreous face. A fibrous matrix is laid down on the posterior vitreous face, serving as a scaffold for more new vessels as they develop. The end result is a fibrovascular sheet adherent to the posterior vitreous face, which, untreated, tends to go through the posterior vitreous face into the vitreous. Fronds of new vessels are now present within the vitreous, either at the disc or elsewhere.

At this stage, the risk is very high that these brittle blood vessels will break, either spontaneously or as a result of vitreous traction. A vitreous hemorrhage is then produced. The size of the hemorrhage is largely dependent on the size of the blood vessel. A mild vitreous hemorrhage may be perceived merely as floaters briefly passing through the field of vision of either eye. As the blood tends to pool down at the bottom of the eye by gravity, the mild vitreous hemorrhage can be seen only for a brief period of time, clearing relatively quickly, in a few hours or days, and giving the patient a false sense of security. If the patient does not seek medical attention at this stage, the neovascular process is allowed to continue further, until a more massive hemorrhage occurs that will cover the macular area. The patient will then note an immediate decline in vision, prompting medical attention.

The natural progression of the proliferative process is the development of a tractional retinal detachment, even if no hemorrhaging has occurred. As the vitreous contracts, it pulls with it the retina at the sites where the new retinal vessels have perforated the posterior vitreous face. A localized retinal detachment occurs that could eventually spread to involve larger areas. If the retina detaches in the periphery, the central vision will not be affected and the patient may not be aware of the changes. However, if the macular area detaches, visual acuity drops immediately, and the patient will then seek medical attention.

If the process is allowed to continue untreated, the neovascular process involves the anterior segment (rubeosis iridis). When the new vessels reach the chamber angle, they produce, as they do elsewhere, a fibrous sheet. The proteinaceous material covers the trabecular meshwork of the angle, thus blocking the outflow of aqueous humor from the eye. This results in drastically increased intraocular pressure (neovascular glaucoma), a difficult condition to treat, which may quickly lead to total blindness. Neovascular glaucoma is accompanied by severe ocular and periorbital pain when the intraocular pressure rises above 50 mg Hg. Neovascular glaucoma is a frequent blinding consequence of uncontrolled diabetic retinopathy.

Treatment

The mainstay of the treatment for diabetic retinopathy in all of its forms is laser photocoagulation of the retina.

Nonproliferative Diabetic Retinopathy. Until recently no satisfactory evidence was available on the treatment of NPDR. In December 1985, a five-year nationwide prospective double-blind study, the Early Treatment Diabetic Retinopathy Study (ETDRS), released its first report, addressing particularly the issue of macular edema. This data showed that focal laser photocoagulation of clinically significant diabetic macular edema substantially reduces the risk of visual loss (Fig. 1). The focal laser treatment is directed at leaking areas within the macula that are demonstrated on fluorescein angiogram. The focal treatment increases the chance of visual improvement, decreases the frequency of persistent macular edema, and causes only minor visual field losses. In this randomized clinical trial, which was supported by the National Eye Institute, 754 eyes that had macular edema and mild to moderate diabetic retinopathy were randomly assigned to focal argon laser photocoagulation, and 1,490 such eyes were randomly assigned to deferral of photocoagulation. The beneficial effects of treatment demonstrated in this trial suggest that all eyes with clinically significant diabetic macular edema should be considered for focal photocoagulation (15).

If no macular edema is present, no treatment is necessary for NPDR. Regular follow-up visits are, however, necessary to keep track of any changes in the fundus findings.

Preproliferative Diabetic Retinopathy. The treatment of prePDR follows the same guidelines as for NPDR, whether or not macular edema is found clinically. Reports on the management of prePDR are still awaited from the ETDRS.

Proliferative Diabetic Retinopathy. Panretinal photocoagulation (PRP; laser photocoagulation of the midperipheral and peripheral retina to exclude the macula) has been unequivocally proven to reduce the risk of blindness resulting for PDR (Fig. 2), as published by the DRS (16, 17) and by other authors (18, 19). The rationale for PRP in the management of PDR lies upon several studies that have shown the role of capillary closure and retinal ischemia in the formation of retinal neovascularization (12, 13). A humoral vasoproliferative factor is released by the ischemic retina, inducing neovascularization (20, 21). Panretinal photocoagulation destroys the ischemic retina and the compromised retina adjacent to the ischemic areas, which in turn eliminates or reduces the stimulus of retinal neovascularization (14). PRP is generally given in about three or four sessions to minimize ocular complications. Only topical anesthesia is necessary in most instances. However, occasionally, retrobulbar anesthesia is required to alleviate the pains that are sometimes associated with its administration.

The side effects of PRP, when given properly, commonly include a reduction of the vision by one or two lines on the Snellen chart, a 10–15 degrees generalized constriction of the visual field, and difficulty in night vision adaptation (22). A reduction of the visual acuity by one line on the Snellen chart was found in 11% of patients

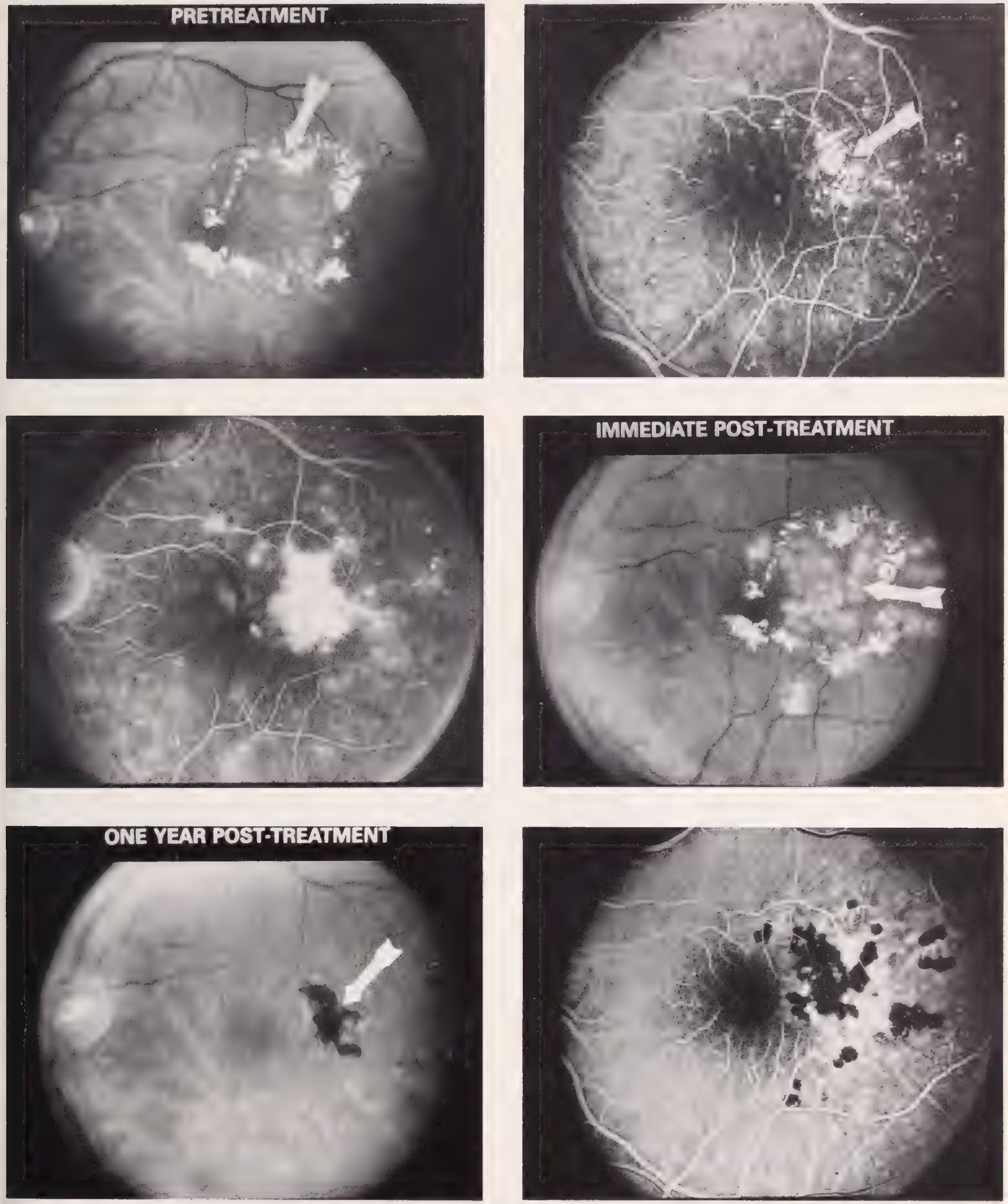

Fig. 1. **Top left** Hard exudates (arrow) disposed circularly, involving center of macula. **Top right** Early phase of fluorescein angiogram showing leakage (arrow) of fluorescein dye in center of circinate of hard exudates. **Middle left** Late phase of fluorescein angiogram showing more diffuse leakage of fluids reaching center of macula. **Middle right** Laser burns (arrow) were given in areas seen to be leaking on fluorescein angiogram. **Bottom left** One year following application of laser burns (laser scars: arrow), total disappearance of hard exudates. **Bottom right** Fluorescein angiography one year after laser treatment showing complete resolution of macular edema.

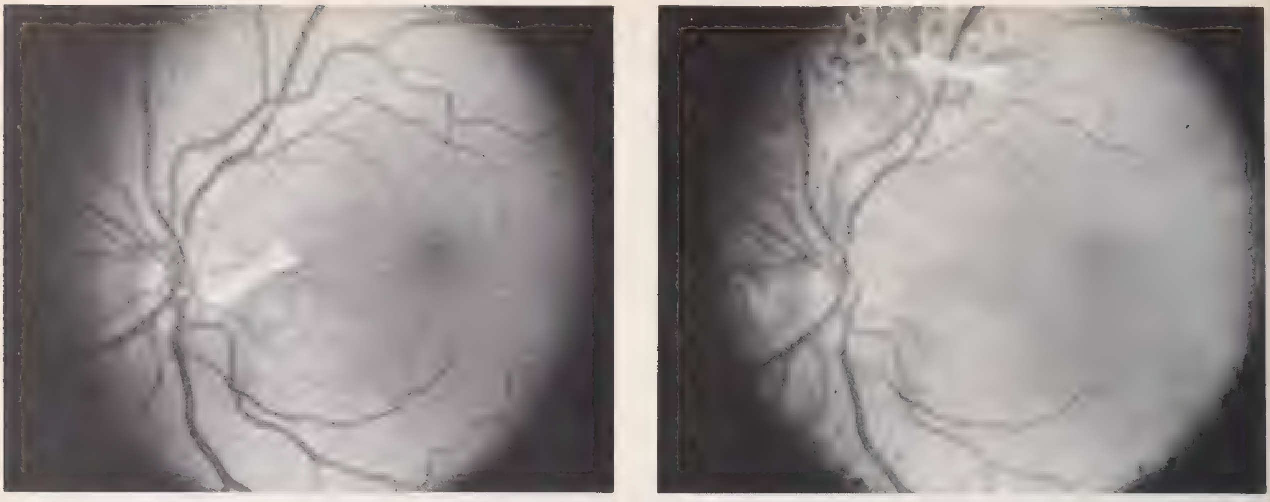

Fig. 2. **Left** Early disc neovascularization (arrow) prior to photocoagulation. **Right** Total regression of disc neovascularization following panretinal photocoagulation. Arrow: laser scars.

treated with PRP, and a modest constriction of the visual field was noted in 5% of patients treated with PRP.

The results of panretinal photocoagulation were clearly favorable compared to the natural course of PDR (11, 16, 23). Zweng, Jack, and Little found a 90% improvement in the appearance of proliferative retinopathy, with a total resolution of new vessels in 50% of the eyes (14). These results parallel those published earlier by the DRS (16). Patients treated with PRP need to remain under surveillance because the neovascular process could resume years later, even following good initial response to the laser treatment and remission of long duration. If neovascularization is noted later on, even years after the initial treatment, additional laser treatment might be necessary to regress the new proliferation.

In those patients who do not respond well to the initial treatment, extensive photocoagulation may be needed, to either control the proliferation or to minimize the magnitude of its complications.

Traction Retinal Detachment. PRP should always be administered when possible in any case of PDR and its complications, including traction retinal detachment. When the macula is not detached, no treatment other than PRP is necessary. However, if the macula detaches, an emergency exists and vitrectomy is warranted to reattach the retina.

In the past decade great advances have been made in the field of vitreous surgery, enabling the surgeon to repair conditions previously considered inoperable, allowing an increase in the proportion of persons saved from total blindness. The proportion of successful reattachment of the retina and improvement of the vision as a result of vitrectomy varies from 50% to 75% among different authors (24–26). However, the complications of vitrectomy are multiple and could actually precipitate the loss of the eye. Surgery is the last resort in the management of the complications of PDR.

Neovascular Glaucoma. Medical management of neovascular glaucoma is temporizing at best. Panretinal photocoagulation is essential to involute the neovascular process of the anterior segment prior to surgery. When the intraocular pressure cannot be controlled by any means, the optic nerve atrophies and total blindness follows. Neovascular glaucoma is generally the endstage and dreaded complication of proliferative retinopathy. It is often the way the diabetic suffers total loss of vision. Continued high intraocular pressure produces corneal edema and constant severe eye pain. A blind, painful eye is treated either via retrobulbar injection of pure alcohol or enucleation.

Medical Treatment and Some Risk Factors

Metabolic Control. One of the most controversial areas in the care of diabetic retinopathy is the issue of "strict" versus "loose" control of blood sugar. To date, the issue is not resolved. Increasing evidence is accumulating in favor of the hypothesis that control of the hyperglycemia makes a difference, at least in the early stages of retinopathy. The available evidence suggests but does not prove that good metabolic control of diabetes may reduce the incidence and severity of diabetic retinopathy. The American Diabetes Association maintains the policy that "optimal regulation of glucose levels should be achieved in the treatment of diabetics, particularly in young and middle-aged individuals who are at greatest risk of developing the microvascular complications" (27).

Diet. No correlation has yet been found between diet treatment of diabetes and the incidence of retinopathy (28). Diet alone has not been shown to reduce macular edema or to improve visual acuity.

Aspirin. Clinical observers have noted that the chronic use of aspirin might be associated with lower incidence of diabetic retinopathy, myocardial infarction, and strokes. The ETDRS has addressed itself to this issue; however, no recommendations have yet been made on the use of aspirin in diabetic retinopathy; evaluation of the data collected in the past five years continues.

Clofibrate. Clofibrate has been shown to reduce the prevalence of hard exudates in diabetics (29, 30). However, this reduction did not result in the improvement of visual acuity; the hard exudates might have already structurally damaged the macula. There was no proof in these studies that the use of clofibrate did prevent the formation of macular edema.

Hypophysectomy. Hypophysectomy was used two decades ago in the management of florid proliferative diabetic retinopathy. However, since the popularization of the laser in the treatment of PDR, and because of numerous side effects of hypophysectomy, this latter method of therapy has been gradually abandoned.

Hypertension. Hypertension is common in diabetics and its fundus manifestations may be similar to that of diabetes. Uncontrolled hypertension tends to increase the exudative process in the retina, thereby worsening diabetic macular edema. Treatment of hypertension alone could improve the macular edema and could make it better responsive to laser photocoagulation. Treatment and adequate control of hypertension in all diabetics is strongly recommended.

Smoking. The effects of smoking are controversial; however, there is a feeling among investigators that smoking exacerbates the ischemic component of the microangiopathy.

Pregnancy. Many diabetic women go through pregnancy without any effect on the retina. Others get worsening of the retinopathy during pregnancy, sometimes leading to the loss of vision. The risk of exacerbation of retinopathy during pregnancy cannot be accurately estimated. The high risk patients are those who start their pregnancy with PDR, whereas those who show none or mild evidence of diabetic retinopathy at the beginning of their pregnancy are not at risk of having their retinopathy worsen. It is recommended that all diabetic women see an ophthalmologist at the first month of their pregnancy. Follow-up is determined by the retinal findings. Laser photocoagulation is also effective and is the first choice of treatment in pregnant diabetics when indicated.

Renal Disease. Renal failure is often associated with an increase in macular edema that does not respond well to laser photocoagulation but to the treatment of the renal failure. Patients undergoing dialysis, particularly vitrectomized or glaucoma patients, seem to be at increased risk of vitreous hemorrhage. The apparent cause of the hemorrhaging seems to lie in the rapid metabolic and blood pressure shifts.

Diagnosis and Referral Guidelines

It is often a hard task for the physician to accurately diagnose treatable retinopathy and refer the patient early enough in the course of the disease to prevent its dreadful complications. The earlier the macular edema or the proliferative changes are noted, the better the chances are for laser treatment to be effective. Although the observation of microaneurysms and/or dot and blot hemorrhages confirms the presence of retinopathy, detecting proliferative changes and identifying those patients who are at high risk for PDR is more complicated. The same is true for macular edema. Besides, there is a poor correlation between the stage of the retinopathy and the level of visual acuity, since visual acuity tests the integrity and the normal functioning of the macula only. A patient might have a severe proliferative retinopathy and yet show evidence of normal vision, if the macula is not involved and if there is no vitreous hemorrhage along the central visual axis, whereas a patient with mild nonproliferative retinopathy but with some degree of macular edema could have impaired vision.

Limits of Direct Ophthalmoscopy. The nonophthalmologist physician is at a clear disadvantage in evaluating the fundi of a patient compared to an ophthalmologist: It is harder to perform direct ophthalmoscopy through a small pupil on a patient who is more likely to have cataract than it is to perform other forms of ophthalmoscopy (indirect ophthalmoscopy and contact-lens biomicroscopy) available to the ophthalmologist. The field of vision of the direct ophthalmoscope is much narrower, and although obvious disc neovascularization may not be missed, peripheral retinal neovascularization, subtle early proliferative changes, and macular edema could very easily be missed particularly when most nonophthalmic physicians do not dilate the pupils.

Type 1 vs Type 2 Diabetes. Some general guidelines to help the physician in assessing the need of referral for ophthalmic care: When a physician is able to detect signs of macular edema or proliferative diabetic retinopathy, prompt referral to an ophthalmologist is advised. But because of the limitations of direct ophthalmoscopy, referral for ophthalmic evaluation should not be based solely on ophthalmoscopic criteria. The referral should also depend on the patient's type of diabetes and the symptoms. The American Academy of Ophthalmology recommends the referral of a type 1 diabetic 5 years after onset, and a type 2 diabetic at the time of initial diagnosis.

Test Corrected Vision in Each Eye. Some ocular symptoms could lead the physician to suspect ocular pathology and assist in the decision to refer the patient. Some basic facts are important to know about our vision.

Patients who are in need of glasses or contact lenses to see normally, such as myopes, hyperopes, or astigmates, will not see well without their glasses. They often say they have "bad" or "very bad" eyes, often a misleading statement meaning only that they cannot see well without their glasses or contact lenses. It is only the best corrected visual acuity that really reflects the status of the macula. Patients should always be asked about their vision with their glasses on.

Once the corrective lenses are in place, it is important to cover one eye at a time to check the vision of each eye separately, even if no eye charts are available. It is surprising how often patients are unaware of any vision change in one eye, particularly when the other eye is still good. This simple maneuver can be an effective screening test at the bedside. It can be done with either the distance or the near correction.

The following are symptoms most commonly encountered in patients having retinal pathology that should prompt referral to an ophthalmologist.

Sudden Onset of Floaters. This is a symptom of major clinical significance. Floaters in the field of vision are very common, and tend to be casually disregarded as benign and not worrisome. When they are long-standing, indeed they are benign. However, when they are of recent and sudden onset, particularly in diabetics, they are often associated with vitreous hemorrhage. They are described as flies, cobwebs, hairs, dark lines or even little red bubbles (RBCs). Even if these floaters are temporary and disappear overnight, they could be due to a mild vitreous hemorrhage that signals PDR. Patients should be alerted about this symptom, because they might get a sense of security if these floaters tend to settle quickly and are not perceived anymore, while the PDR is progressing unattended. They should be encouraged to check one eye at a time to try to identify the eye that is having the floaters.

Flashing Lights (Photopsia). The flashing lights are spontaneous brief light sensations, sometimes colorful. They represent irritation of the retina generally due to vitreous traction. In a diabetic patient, these might herald proliferative retinal changes, particularly if they are associated with floaters.

Defects in Visual Field. A visual field cut is a serious complaint. It is described as an inability to see one side of the visual field of one or both eyes, as if covered by a shadow, or a curtain. The etiology can be varied, including multiple retinal conditions. It should be considered as an emergency unless its cause is well known to the patient for a long time.

Sudden Blurring. A sudden blur of the vision is a symptom that requires immediate attention by an ophthalmologist. It is a loss of function of the eye which should be investigated as soon as possible.

Once the patient has been referred to the ophthalmologist, the frequency of follow-up examinations is determined by several factors. A yearly examination is sufficient for some patients; others must be seen monthly or bimonthly, depending on the stage of the retinopathy.

Summary

It is thanks to prospective double-blind randomized clinical trials such as the DRS and the ETDRS that we can now reduce by at least half the amount of moderate to severe visual loss caused by diabetes. Ongoing clinical trials such as those assessing the effects of aspirin, aldose reductase inhibitors, and tight control of blood glucose may provide more preventive measures

in the concentrated effort to reduce the risk to vision posed by diabetes. But until further progress is made, photocoagulation remains our main tool in our struggle to avert visual loss in diabetic retinopathy. "With every new announcement of its value, we must make sure to include the message that it is effective only for patients who are referred in time" (31).

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Impotence in Diabetic Men

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Erectile dysfunction is a relatively common problem in adult diabetic men. Although this complication was initially described in 1798 (1), little systematic study of the problem or its pathogenesis was carried out prior to 1950. The development during the last three decades of tools to evaluate the neural, vascular, and hormonal contributions to the process of erection has resulted in increased understanding of the pathophysiologic processes involved in impotence in the diabetic patient. Concomitantly, advances in sex therapy, the use of new pharmacologic agents, and improvements in penile prosthesis have resulted in restoration of satisfactory sexual activity in many diabetic men who develop sexual dysfunction.

Prevalence. The prevalence of impotence in diabetic men averages approximately 40%, with a range of 27.5% to 75% in various studies (Table) (2–13). The prevalence increases with age, and in men under 75 years is manifold higher than that found by Kinsey and co-workers in their large cross-sectional population study (14) (Fig.). Although many authors have compared the frequency of impotence in diabetic men with the Kinsey data, this comparison may not be entirely appropriate, since many of the studies used different criteria for defining impotence. Thus, impotence has been defined as frequent or constant difficulties in obtaining or maintaining an erection (4, 6), as an erection that is not firm enough to successfully conclude the act of coitus (8), as six months of partial or complete failure to obtain an erection (12), or as failure to achieve adequate erection in 25% or more attempts at intercourse (15). This problem could certainly have been overcome had the studies used concurrent controls rather than relying on historical data. In addition, there is evidence that patients attending general medical clinics may actually have a higher prevalence of impotence than has been previously appreciated. Lester and associates (16) found that 23% of their diabetic males have suffered from impotence and that 20% of 50 nondiabetic hospital outpatients also had similar complaints. Similarly, Slag and co-workers (17) found that 34% of 1,180 men in a medical outpatient clinic were impotent. Again, this points out the need for concurrent controls in interpreting the studies dealing with the prevalence of impotence in diabetic men.

Proposed Etiologies. The attainment of a normal erection requires the functional integrity of the central, peripheral, and autonomic nervous systems, adequate arterial blood supply to the penis, and an intact hypothalamic-pituitary-gonadal endocrine axis. Psychogenic or erotogenic stimuli originating or perceived by the cerebral cortex are transmitted to the limbic system and then to the thoracolumbar (T12-L3) sympathetic tract. The sympathetic nerves appear to facilitate erection and are primarily involved in smooth muscle contractions during emission and ejaculation. Tactile genital stimuli initiate a spinal reflex arch with the afferent limb located within the pudendal nerves, which stimulates the sacral parasympathetic nerves (S2-S4), which in turn results in dilatation of the arteriolar vessels that supply the corpora cavernosa and spongiosum. Contraction of the ischiocavernosa muscle leads to compression of the veins draining the corpora cavernosa and spongiosum and, together with the increased arterial blood supply, results in distention, engorgement, and rigidity of the penis.

Various etiologies for the impotence seen in diabetic men have been proposed. As noted above, some investigators have found a similar frequency of impotence in diabetic and nondiabetic patients attending medical clinics, sug-

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gesting that impotence may be relatively frequent in many acute or chronic illnesses. However, the prevailing view is that impotence in diabetics results from neurologic dysfunction of the pelvic autonomic nerves, vascular insufficiency, psychological problems, or medications used to treat the hypertension so frequent in these patients. In many instances, the impotence may be multifactorial, with contributions from neuropathic, vasculogenic, and psychiatric problems.

There exists a large body of epidemiologic data suggesting that the major cause of diabetic impotence is a visceral neuropathy of the sacral parasympathetic outflow to the penis. Many studies have demonstrated that diabetic patients with impotence have an increased frequency of peripheral neuropathy as well as autonomic neuropathy. Since the autonomic neural innervation of the bladder and penis are similar, an association between diabetic cystopathy and impotence would be anticipated, and indeed has been demonstrated by Ellenberg (8). Prolongation of the bulbocavernosus reflex latency time, absence of the normal reflex contraction of the bulbocavernosus and ischiocavernosus muscles in the perineum following brisk manual compression of the glans penis, and diminished testicular sensation have also been demonstrated in diabetic men with impotence (18, 19). Decreased spontaneous electrical activity of the bulbocavernosus and ischiocavernosus muscles during sleep have also been noted, again indicating a neuropathic process (20). The findings of significantly reduced urine flow rate in impotent diabetic men in comparison to diabetic patients without impotence also suggests that neuropathic processes may be involved, although hesitancy and altered flow rate may be psychogenic in origin (21). Histologically, abnormalities of autonomic nerve fibers in the corpora cavernosa of patients with diabetic impotence have been demonstrated (22). Finally, reduced concentrations of norepinephrine in the corpora cavernosa of type 1 diabetic patients have been found, suggesting an impairment of penile sympathetic innervation (23).

TABLE

Prevalence of Impotence in Diabetic Men

Author (Reference)	Year	N	% Impotent
Rundles (2)	1945	69*	28
Martin (3)	1953	70*	54
Rubin & Babbott (4)	1958	198	55
Montenero & Donatone (5)	1962	436	36
Schoffling et al (6)	1963	314	53
Prikhozhan (7)	1967	350	75
Ellenberg (8)	1971	200	59
Faerman et al (9)	1972	299	40
Kolodny et al (10)	1974	175	49
Neubauer & Schoffling (11)	1977	146	43
McCulloch et al (12)	1980	541	35
Lipson (13)	1984	260	53

* Diabetic patients with neuropathy.

Vascular insufficiency may certainly cause impotence in some diabetic men. Macrovascular disease involving the bifurcation of the aorta may lead to claudication and impotence (Leriche syndrome). Angiographic studies of impotent diabetic males with leg ischemia have shown a greater degree of stenosis of the internal pudendal arteries than in nonimpotent patients with leg ischemia (24). Several studies have demonstrated abnormalities in penile blood pressure and blood flow by noninvasive Doppler techniques (21, 25–27). However, a recent study has suggested that the prevalence of abnormalities in Doppler penile arterial pulse sounds and wave forms is similar in diabetic men without impotence and in those with impotence (21). This suggests that penile vascular problems may be frequent in diabetic patients and are not of sufficient magnitude in the majority to be the sole etiologic factor.

Numerous studies have evaluated the hypothalamic-pituitary-testicular axis in impotent diabetic men and have failed to demonstrate a consistent abnormality. Thus, normal levels of serum testosterone, testosterone-estradiol-binding globulin, free testosterone, luteinizing hormone, follicle-stimulating hormone, and pro-

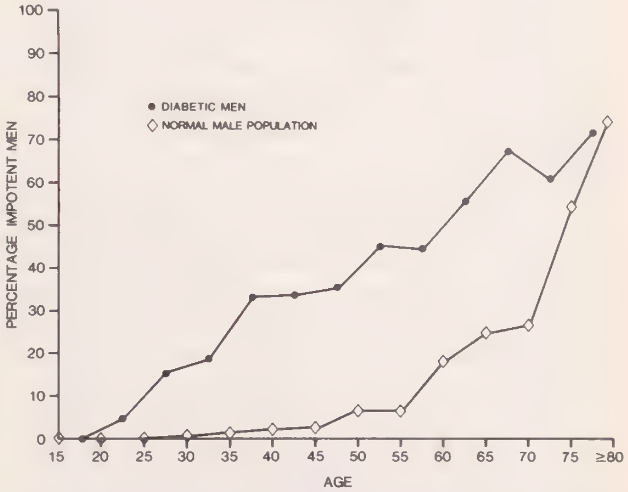

Fig. 1. Incidence of impotence in diabetic men compared with general population. Data for diabetic patients derived from combined data in references 4, 5, 10, and 12; total of 1,353 subjects. Data for normal population is from cross-sectional study of Kinsey et al (14).

lactin are usually found (8, 10, 28–33). Several studies have examined gonadotropin responsiveness to gonadotropin-releasing hormone; in most instances, the response has been normal (29, 32). A few studies have demonstrated minor abnormalities in comparison to controls (33, 34). It is of interest that Zeidler and co-workers (33) found a decrease in the luteinizing hormone concentrations following gonadotropin-releasing hormone at 30 min and 150 min in impotent diabetic men in comparison to nonimpotent controls. These abnormalities reverted to normal following lowering of the blood sugar, suggesting hyperglycemia per se was responsible for the minor abnormalities noted during the test. Finally, treatment of impotent diabetic males with testosterone does not alter the impotence, again indicating that androgen deficiency does not play a role in the pathogenesis of diabetic impotence (8).

In addition to the above factors, diabetic men may also develop impotence as a nonspecific response to the catabolism associated with the acute metabolic disturbances that occur at the onset of diabetes mellitus (4, 6, 9). Such impotence is generally transient and resolves within one year following attainment of good diabetic control. This form of impotence may be present at the onset of symptomatic diabetes in 8%–13% of diabetics (8, 10). Diabetic men may also develop psychogenic impotence, although it is not clear if the presence of chronic illness such as diabetes predisposes these individuals to psychologically mediated impotence (21, 35–37). Some diabetic men clearly have a remarkable response to sex therapy (37). Finally, in diabetic patients the prevalence of hypertension is 2–3 times greater than in the general population, and impotence may be a side effect of medications used for treating hypertension (13). Switching a patient to a drug such as prazosin entailing low risk for inducing impotence may alleviate the sexual dysfunction (13).

Clinical Features. Impotence in diabetic men may occur at or shortly following onset when the patient is experiencing acute metabolic alterations, but the more common form has a gradual onset, with slow progression over 6–24 months. Initially, the patient notes a decrease in either the strength, firmness, or duration of erection, both during intercourse and masturbation. Many patients also note a loss of pumping sensation during ejaculation, and approximately half develop impairment of early morning erections. The frequency of erection diminishes and, finally, erections are lost. Approximately a third of patients carefully questioned note a seepage of seminal fluid out of their erect or flaccid penis at or before orgasm. Initially, libido is maintained, but this may also wane in patients as a secondary phenomenon due to sublimation (8, 10, 35, 38). Nocturnal penile tumescence studies have confirmed that diabetic men complaining of impotence have a smaller number of tumescent episodes, a decreased amount and frequency of maximal tumescence, and a lower than normal maximum penile circumference change during erections, and spend a significantly shorter time in the erect state than do normal controls (39). Thus, the presentation of impotence in diabetic men is different from that in patients with classical psychogenic impotence, who have an abrupt onset of erectile loss associated with low libido, maintenance of morning erections, and differential firmness of erections dependent on the type of sexual stimuli and/or situational factors (8, 40).

Diabetic impotence is not associated with severity of diabetes (4), insulin dose (6), degree of diabetic control (12, 30), type of therapy (41), duration of diabetes (8, 10), coexistence of hypertension (10), nephropathy (10, 12), retinopathy (4, 10, 30), or the presence of peripheral vascular disease (4, 6). The most consistent abnormality associated with impotence is the presence of peripheral and autonomic neuropathy. Peripheral neuropathy may be manifested by glove-and-stocking hypoesthesia, especially in the lower extremities, with decreased sensation to pinprick and diminished vibratory sense. There may be an associated absence of the Achilles tendon reflex. Autonomic neuropathy may be manifest by postural hypotension and diabetic cystopathy with decreased frequency of urination, increased volume of urine, slow stream of urine, or urinary retention with overflow incontinence. In addition, there may be disturbances of gastrointestinal motility with constipation or nocturnal diarrhea and nausea and vomiting from gastroparesis. Anhydrosis in the lower limbs, gustatory sweating, hypoglycemic unawareness, resting tachycardia, and slow pupilary reflexes may also be seen (1, 12).

Diagnosis. In most instances, a careful history and physical examination should suffice in differentiating between organic and psychogenic impotence. A diabetic man with slowly progressive erectile dysfunction who has physical findings of peripheral and autonomic nervous system neuropathy should present little difficulty in correct diagnosis. Nevertheless, we generally perform a number of evaluations in order to confirm the presence of an organic lesion and evaluate the patient for the possibility of primary or coexistent correctible abnormalities that may be contributing to the impotence. Normal men have 3–5 erections a night associated with rapid eye movements in sleep. Such nocturnal penile tumescence can be monitored with strain gauges placed behind the glans penis and at the base of the penis. Absence or reduced frequency of nocturnal tumescence indicates an organic lesion. This type of test is useful for defining the number and duration of erections per night and the changes in circumference of the penis during erection. However, nocturnal penile tumescence monitoring cannot assess the rigidity of the erection. Rigidity may be tested by the use of a snap-gauge band that wraps around the penis and contains three small plastic strips attached to it (Snap-Gauge, Dacomed Corp, Minneapolis, MN 55420). Each of the color-coded strips breaks at a different tension (42).

Penile blood pressure may be evaluated by Doppler ultrasound during deflation of a small pneumatic cuff wrapped around the base of the penis. The ratio of penile blood pressure to brachial artery blood pressure is greater than 0.75 in normal persons, whereas patients with vasculogenic impotence generally have values under 0.60 (43). This type of measurement should also be performed following 3 minutes of lower extremity and buttocks exercise to determine whether blood is diverted away from the penis during exercise (pelvic steal syndrome).

Although hyperprolactinemia and hypogonadism are not responsible for impotence in the majority of diabetic men, those conditions are sufficiently common causes of impotence to warrant screening for them. Therefore, serum free-testosterone level and prolactin should be measured. It is important to remember that testosterone concentrations fluctuate frequently during the day, and therefore one should obtain three blood samples at 20-minute intervals and combine equal aliquots of the serum before performing the testosterone assay in order to compensate for this fluctuation (44). Tests of thyroid and liver function and an assessment of renal function should also be carried out, since both hyper- and hypo-thyroidism, hepatic insufficiency, and renal insufficiency may result in impotence.

Therapy. As noted above, impotence in diabetic patients may be multifactorial. Thus, autonomic neuropathy, vascular insufficiency, psychogenic factors, and illicit drugs, alcohol, or medications may have an additive effect and result in erectile dysfunction. Alcohol use should be discontinued, as should antidepressants. Impotence may be associated with such antihypertensive agents as diuretics, chlorthalidone, methyldopa, clonidine, reserpine, guanethidine, spironolactone, propranolol, and hydralazine (13). Switching to the alpha$_1$-adrenergic blocking agent, prazosin, may alleviate drug-induced impotence. Hypogonadism generally responds to testosterone replacement therapy, and hyperprolactinemia may be treated with the long-acting dopamine agonist bromocriptine. Phenoxybenzamine (an alpha-adrenergic blocker) has also been found to be useful in some patients. Recently, erections have been induced in patients with organic impotence by the intracavernous injection of papaverine, which leads to vasodilatation of the penile vasculature (45). This latter therapy must still be considered experimental.

Vasculogenic impotence associated with aortoiliac and hypogastric artery lesions may be improved by vascular surgical correction. Lesions of the penile vessels have been treated with microsurgical revascularization techniques, but the success rate thus far has been disappointing.

Sex therapy clearly has a role in the treatment of diabetic impotence. First, impotence in a diabetic man may be primarily psychogenic. Certainly, anxiety and depression may be seen in any patient with a chronic illness. Second, because impotence is a well-known complication of diabetes, diabetic men may develop impotence as a "self-fulfilling prophecy." Finally, minor erectile dysfunction in a diabetic patient may be magnified by performance anxiety. Sex therapy may be quite beneficial in each of these situations and should be considered prior to implantation of a penile prosthesis (37, 46) Since the sensation of orgasm may persist despite the inability to achieve an erection, the sexual satisfaction of both the patient and his partner may be possible through other means.

If these measures are inappropriate or inadequate for a patient who has well-established organic impotence, surgical implantation of a penile prosthesis should be considered. Several studies have shown that diabetic males have a satisfaction rate over 90% following implantation of the prosthesis and a complication rate similar to that in nondiabetic impotent patients undergoing such surgery (40, 47).

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Peripheral Vascular Disease in Diabetic Patients: Evaluation and Treatment

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It is generally accepted that diabetes mellitus predisposes to atherosclerotic vascular disease affecting the lower extremities. Atherosclerosis is more common in diabetics, occurs at an earlier age, and is more extensive (1). In nondiabetics, atherosclerosis is more prevalent in males, but in diabetics the sexes are equally affected. The pattern of vascular disease also differs in the two populations; diabetics have a higher incidence of tibial and peroneal artery disease and more extensive arterial calcification than nondiabetics. (2). However, the atherosclerotic lesion in the arteries of diabetics is indistinguishable from that found in nondiabetics (3).

The initial symptom of occlusive vascular disease is intermittent claudication which can progress to rest pain and gangrene. In nondiabetics, symptomatic vascular disease rarely leads to amputation, but in diabetics once the disease is clinically manifest it often progresses rapidly (4). Overall, diabetics have a risk of amputation 15 times greater than nondiabetics (5), and once a limb is amputated there is a 30% to 50% incidence of gangrene affecting the remaining limb (2, 6, 7). A recent report suggests the risk of amputation for noninsulin-dependent diabetics is less than for insulin-dependent diabetics (8). Gangrene is more frequent in diabetics because of their susceptibility to infection, extensive vascular disease, and neuropathy which makes them vulnerable to foot trauma. The goal of evaluation and treatment of vascular disease in diabetics is to keep the patient ambulatory and functional and avoid amputation.

Risk factors for atherosclerosis include duration of diabetes, hypertension, smoking, obesity, and emotional stress (1, 9, 10, 11). Accelerated atherosclerosis is known to occur in patients with diabetes mellitus but the pathway responsible for this complication is unknown. Diabetic patients with atherosclerosis often have hypertriglyceridemia and an increased body pool of low-density lipoprotein (LDL). It has been shown that LDL is a risk factor for atherosclerosis and increased levels of high-density lipoproteins (HDL) are associated with less atherosclerosis (9). Insulin-dependent diabetics who are poorly controlled have decreased levels of HDL, and those well controlled have higher levels of HDL. However, some noninsulin-dependent diabetics have low levels of HDL and severe atherosclerosis (12).

There is a tendency for diabetics to be hypercoagulable, which aggravates their vascular disease. Diabetics tend to have increased platelet adhesiveness, and studies suggest increased levels of serum fibrinogen (9). Infection in ischemic tissue is difficult to treat, and diabetics have an increased susceptibility of infection.

Clinical Evaluation

The signs and symptoms of vascular disease affecting the lower extremities are intermittent claudication, ischemic rest pain, nonhealing wounds of the feet, and gangrene. Intermittent claudication is a muscle discomfort, described as a cramp, ache, or tiredness brought on by exercise and relieved rather promptly by rest. Usually standing still will relieve the pain and if the patient must sit for relief the physician should consider the pain may be pseudoclaudication from spinal stenosis. Aortoiliac occlusive disease causes claudication of the buttock, hip, and thigh and femoral-popliteal occlusive disease causes calf claudication. Occasionally, a patient will experience foot claudication from tibial and peroneal artery disease. Thus, the location of the

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patient's pain will often point to the arteries affected.

Vascular examination of the lower extremity includes palpating the pulses of the aorta and of the femoral, popliteal, dorsalis pedis, and posterior tibial arteries. It is helpful to grade the pulse, using 3+ as normal, 2+ as mildly diminished, 1+ as markedly diminished, and 0 as absent. Bruits over the aorta and femoral arteries are noted, recognizing that a bruit indicates turbulent flow and does not relate to degree of stenosis. An occluded artery does not have a bruit. The feet must be examined for wounds and skin nutrition. In chronic ischemia there is loss of subcutaneous tissue, demonstrated on the heel and big toe by a residual indentation of the skin after finger pressure. The toes should be separated to look for fungal infection and "kissing ulcers," and the heels examined for cracks and fissures. The ischemic foot pales on elevation and becomes ruborous on dependency.

Occasionally a patient with iliac artery stenosis will have a history of intermittent claudication and palpable distal pulses. A maneuver that diagnoses this condition is to have the patient walk until symptoms occur and then examine the feet. The foot on the involved side will be pale and the pulse will have disappeared.

The ankle blood pressure is measured over the dorsalis pedis and posterior tibial arteries using a Doppler ultrasound recorder. The ankle pressure is compared to the arm blood pressure, creating an ankle-brachial index. The normal ankle-brachial index is 1.0 or slightly higher. An ankle-brachial index less than 1.0 indicates proximal disease and an index less than 0.5 indicates advanced ischemia. Diabetics may have calcification of the tibial arteries which prevents compression and gives a falsely high ankle blood pressure, often much higher than the arm pressure.

On occasion the diagnosis of peripheral vascular disease can be difficult, especially if the patient has palpable pulses and other diseases causing pain in the legs, such as spinal stenosis or lumbosacral disc disease. Under these conditions the vascular laboratory is helpful because it can accurately determine the status of the arterial circulation. Using the Doppler ultrasound recorder, segmental pressures are measured at the proximal and distal thigh, calf, and ankle and compared to the arm pressure. A pressure gradient localizes the area of arterial stenosis or occlusion.

Segmental plethysmography using a pulse volume recorder (PVR) detects arterial disease by evaluating the arterial wave form during systolic expansion at different levels of the extremity. The PVR is not influenced by rigid arteries and can be used for patients with arterial calcification.

The walking claudication test and Doppler femoral artery wave form analysis are most useful in the differential diagnosis of occlusive vascular disease. The walking claudication test monitors the ankle blood pressure with the patient exercising and is more objective than the walking test described for the office. In normal patients the ankle blood pressure rises with exercise. A fall in ankle blood pressure indicates proximal arterial obstruction. The femoral artery wave form analysis detects iliac artery obstruction and is useful when the patient has a good resting femoral pulse. The normal wave form has a sharp upstroke during systole and reversed flow in early diastole. With proximal obstruction there is initial loss of the reversed flow, and with more severe obstruction blunting of the systolic curve (Fig.).

The laboratory can also assist in determining the level for amputation in patients with gangrene. Healing of digit and transmetatarsal amputation correlates better with digit pulsation and blood pressure than with ankle blood pressure. However, caution is advised in trying to predict level of amputation solely by hemodynamic indices (13).

Arteriography is reversed for patients considered for surgical intervention or balloon angioplasty. Arteriography is not required for the diagnosis of vascular disease but is used to determine the best surgical approach. If arteriography is performed the arterial system is visualized from the renal arteries to the ankles, although on occasion visualization from the groins distally is sufficient. The arteriogram is usually done by retrograde catheterization of the femoral artery. If the patient has severe iliac disease, the translumbar approach is used. Recently, outpatient intraarterial digital subtraction arteriography (DSA) has become available. The DSA technique has an advantage in diabetics with nephropathy because it uses smaller amounts of nephrotoxic contrast solution. Venous DSA is not advised because of inadequate visualization of the distal arteries and the need for a larger bolus of dye.

Treatment

Treatment is divided into three phases: prophylaxis, nonoperative, and surgical intervention.

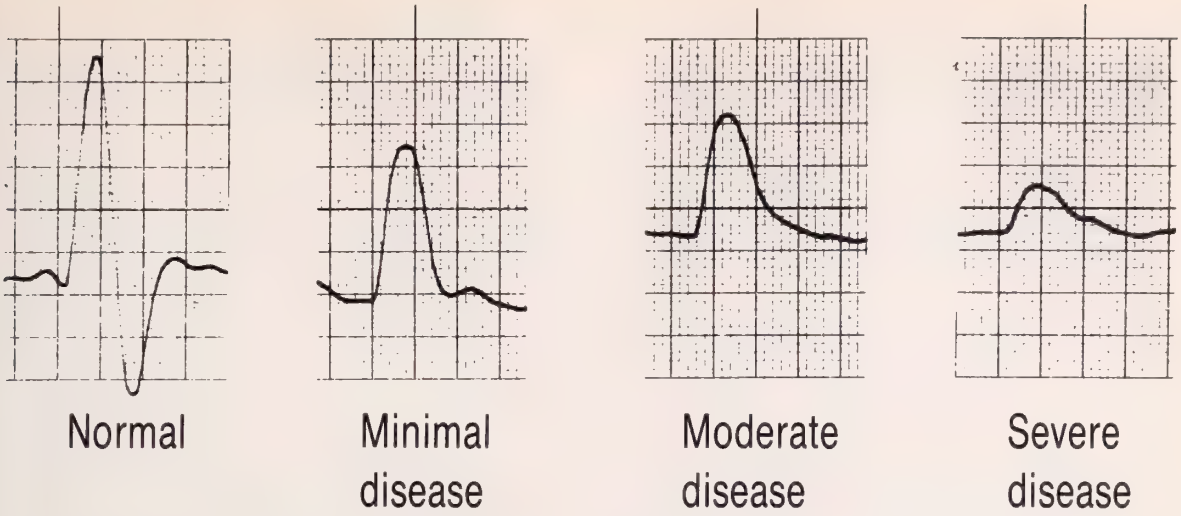

Fig. Recordings of Doppler femoral artery waveform with increasing degree of stenosis.

Prophylaxis. The hallmark of prophylaxis is patient education. It has been shown that a patient educated on good foot care who takes meticulous care of his or her feet has less risk of amputation or hospitalization for foot problems (14, 15, 16). The diabetic foot must be examined every day by the patient or another person if the patient has diminished vision. The diabetic is instructed to bathe the feet daily in lukewarm water, dry carefully, wear soft comfortable shoes, and be wary of new shoes. Stiff new shoes can abrade the skin, and the diabetic with sensory neuropathy may not be aware of the irritation until a wound develops. Toenails should be cut straight across and ingrown nails trimmed by a physician or podiatrist. The diabetic should never go outdoors barefoot, and must avoid the extremes of hot and cold. Any foot wound is reported to a physician immediately. Patients with intermittent claudication are instructed to walk a set distance once or twice a day, temporarily stopping when discomfort occurs.

A variety of drugs have been tried in the hope of improving blood supply to the lower extremities. Vasodilators such as papaverine, nicotinic acid, tolazoline, reserpine, and nylidrin have been used without documented benefit. The Federal Drug Administration (FDA) has stated that these drugs are not effective for the treatment of intermittent claudication, and the use of vasodilators has been discontinued. Pentoxifylline has recently been approved by the FDA. Pentoxifylline lowers blood viscosity and increases erythrocyte deformability, thereby improving blood flow and oxygen delivery. Although studies find intermittent claudication is improved with pentoxifylline (17), I think the drug has limited benefit.

If a foot wound develops, all trauma to the area must be avoided. A small piece of lamb's wool or cotton between the toes protects the toes from rubbing against one another, a cause of "kissing ulcers," and helps treat interdigital fungus infection. Wounds on the plantar surface may require bed rest because weight-bearing is a form of trauma. Wounds adjacent to ingrown toenails are treated by elevating and trimming the nail. All wounds must be cleansed daily with lukewarm water and covered with povidone-iodine or a local antibiotic. Wounds that fail to heal because of ischemia require improved blood supply, which can only be obtained by surgical intervention.

There are a variety of surgical options depending on the site of arterial occlusion and patency of the distal vessels. Sympathectomy is reserved for patients who have sympathectic tone, who are not eligible for direct arterial surgery, and who do not have neuropathy. Diabetics with neuropathy have an autosympathectomy; surgical sympathectomy will not be useful. In general, sympathectomy has been shown to have limited success for treatment of vascular disease in diabetics (18), and I rarely advise sympathectomy. Percutaneous balloon angioplasty is used to treat localized stenosis of the iliac artery and, on occasion, of the superficial femoral artery. Dilatation of the more distal arteries is rarely successful and may be dangerous.

The best result will be obtained by direct arterial surgery. Whenever possible the bypass technique should be used from an artery with good input to an artery patent to the foot. However, in many instances the distal anastomosis will be to a vessel that is not in continuity to the foot, including an isolated popliteal artery. Under this condition, despite the distal disease, grafts will function (19, 20) and the foot can be improved. Synthetic grafts are used to bypass aortoiliac disease, and saphenous veins, either reversed or nonreversed, are used to bypass femoral, popliteal, and tibial artery disease. Today, the bypass operation has been extended to the distal tibial and pedal arteries with good results (21, 22, 23).

After arterial revascularization, small areas of gangrene will autoamputate and larger areas are treated by toe, ray, metatarsal or Syme amputation. If a patient has extensive gangrene involving the foot it may be preferable to do a primary amputation. Although amputation is a less desirable result than successful revascularization, with today's improved prostheses the amputee can ambulate and resume a meaningful life style (24).

Summary

Diabetics have an increased risk of amputation because of a greater incidence and severity of vascular disease and susceptibility to infection. To lessen the risk of amputation, diabetics must take excellent care of their feet, including daily inspection and wearing proper shoes. Any wound can become limb-threatening and must be reported to a physician immediately and treated vigorously. Nonhealing wounds require improved blood supply, which is best accomplished by direct arterial surgery. Today, the bypass operation can be extended to the distal tibial and pedal arteries with good results. Following revascularization, small areas of gangrene will autoamputate and larger areas are treated by surgical amputation. Extensive gangrene is best treated by primary amputation.

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Lipid Disorders in Diabetes Mellitus

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Hyperlipidemia is commonly observed in diabetics, especially in patients under less than adequate metabolic control. This association between hyperlipidemia and diabetes is of great concern because of the potential for the development of macrovascular disease. In both insulin-dependent (type 1) and non-insulin-dependent (type 2) diabetic patients, atherosclerosis is accelerated, and the complications of atherosclerosis are the leading cause of death (1). In addition, hyperlipidemia is probably an additional independent risk factor for atherosclerosis in diabetes and thus serves to further accelerate macrovascular disease (2–4).

In this review, some of the more important lipid phenotypes that occur in diabetes are highlighted and their management is discussed. In addition, the pathophysiology of atherosclerosis is discussed in relation to recently described lipid abnormalities in diabetes that are not readily apparent from plasma lipid levels.

Overview of Lipid Metabolism

Triglyceride-rich lipoproteins enter the plasma from two different sources and ultimately have different fates (5). Chylomicrons are secreted by gut epithelial cells directly into lymphatics. These large particles are composed of a hydrophobic core of dietary triglyceride and cholesterol ester, as well as the apoproteins C, E, and B-48 (Fig. 1). Apo C is a specific activator of the enzyme lipoprotein lipase (LPL), which is located on the capillaries of many tissues, but especially those of adipose tissue and skeletal muscle. LPL breaks down the triglyceride into free fatty acids (FFA), which are then taken up by the cells and used for storage of energy. The result of this hydrolytic process is a smaller particle, called a chylomicron remnant. Apo C has been consumed by the LPL reaction, and the apo E directs the particle to a specific receptor on the liver that recognizes apo E, hence referred to as the chylomicron remnant receptor (6). This receptor is present in patients with homozygous familial hypercholesterolemia and hence is distinct from the apo B-100:E receptor (discussed below). The chylomicron remnant is then taken up by the liver, and the cholesterol contained within the particle enters the intrahepatic cholesterol pool.

Very low density lipoprotein (VLDL) is synthesized by the liver from lipid that is produced endogenously. VLDL contains apo C and E, as well as a different form of apo B: B-100. This triglyceride-rich particle is also catabolized by LPL and converted into a particle containing apo B-100 and apo E called intermediate-density lipoprotein (IDL). However, the fate of IDL is different from that of the chylomicron remnant. IDL is recognized by the same hepatic and peripheral receptors that recognize low-density lipoprotein (LDL). This receptor species specifically recognizes apoproteins B-100 and E and is deficient or defective in familial hypercholesterolemia. Some IDL is taken up by endocytosis via hepatic apo B-100:E receptors and catabolized. Other IDL particles are not taken up and catabolized but interact with the liver in an as yet unclear manner. After losing most of their triglyceride and all apoproteins except for apo B-100, these particles are converted into LDL. LDL contains most of the cholesterol that circulates in plasma and has apo B-100 as its primary apoprotein. Because of the presence of apo B-100, LDL is recognized by apo B-100:E receptors in hepatic and peripheral

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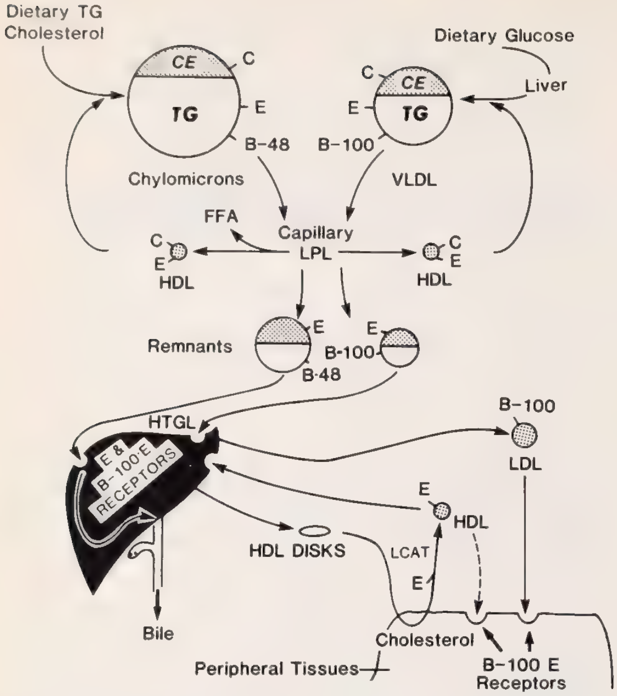
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B-100
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HDL DISKS
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Fig. 1. General schema of lipoprotein metabolism. Abbreviations: CE, cholesterol ester; TG, triglyceride; VLDL, very low density lipoprotein; LDL, low density lipoprotein; HDL, high density lipoprotein; LPL, lipoprotein lipase; HTGL, hepatic triglyceride lipase; FFA, free fatty acids; LCAT, lecithin: cholesterol acyl transferase.

tissues, and hence delivers cholesterol for maintenance of cell membranes.

High-density lipoprotein (HDL) is important in several aspects of lipid metabolism. During LPL-mediated triglyceride hydrolysis, HDL recycles the LPL-cofactor apo C back to newly formed chylomicrons and VLDL. In addition, HDL mediates the net reverse transport of cholesterol from peripheral cells back to the liver (Fig. 1). After being secreted by liver, HDL interacts with peripheral tissues, acquires free cholesterol and apo E, and activates lecithin cholesterol acyl transferase (LCAT). LCAT converts free cholesterol into cholesterol ester, resulting in a cholesterol-enriched particle containing apo E. Because of the presence of apo E, HDL can now be recognized by hepatic apo E or B-100:E receptors. Hence, HDL can effect a net transport of cholesterol back to the liver.

Serum Lipid Levels in Diabetes

Many studies on lipid levels in diabetic patients have been difficult to interpret because of insufficient documentation of clinical criteria such as type of diabetes, age, weight, and degree of metabolic control. Fig. 2 shows the results of a

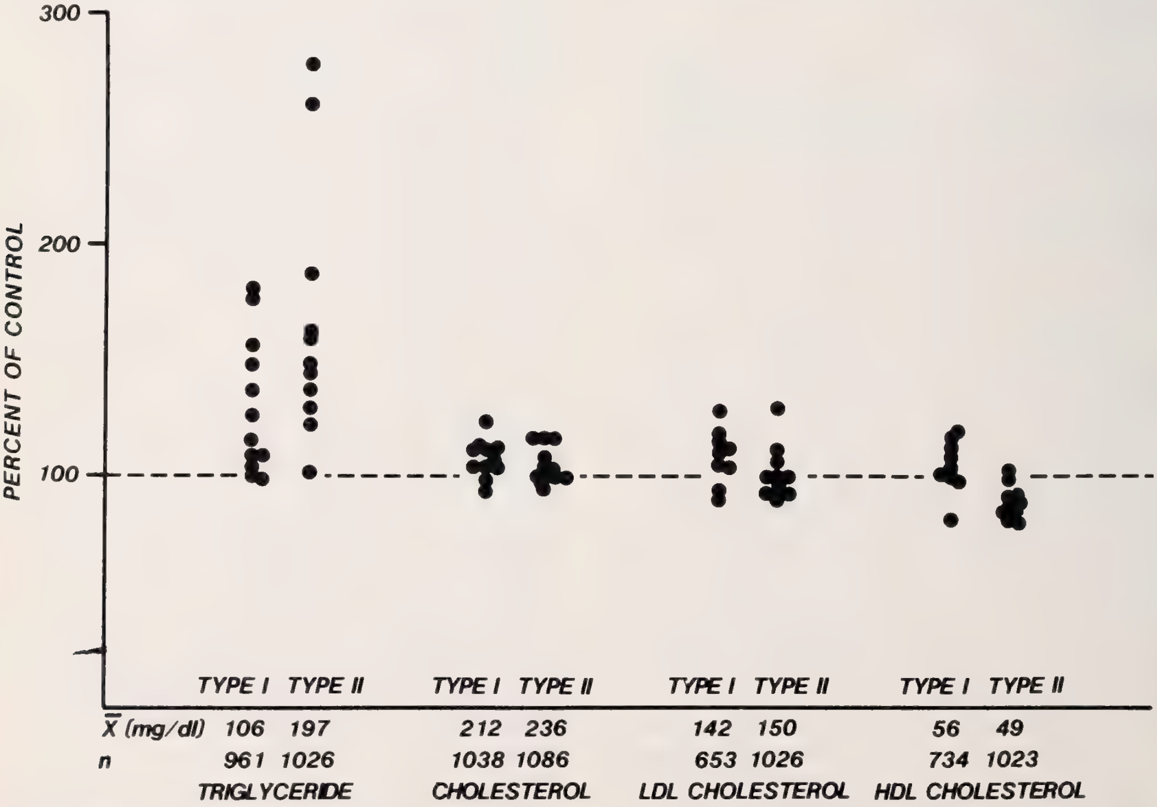

Fig. 2. Plasma lipid levels in insulin-dependent (type 1) and non-insulin-dependent (type 2) diabetic patients. Lipid values were obtained from 22 studies since 1978 in which diabetic patients were compared to a control group matched for age and weight. All patients were undergoing some form of treatment, each study clearly defined patients as insulin-dependent or non-insulin-dependent, and each study involved at least 13 patients. Each point represents mean values of diabetic patients divided by mean values of controls. A listing of the studies is available upon request.

literature survey which attempts to pool the data from 22 interpretable studies over the last 10 years. Each study involved at least 13 patients who were clearly defined as insulin-dependent or non-insulin-dependent, and were on some form of adequate therapy. In addition, each study included a control population that was matched for age and weight. As can be seen, the major lipid abnormality in diabetic patients is mild hypertriglyceridemia, whereas hypercholesterolemia is generally not a common feature. Interestingly, insulin-dependent (type 1) diabetics usually have normal or elevated levels of HDL. One study has suggested that much of this elevated HDL is the HDL_2 subfraction (7). It is the HDL_2 subfraction that correlates best epidemiologically with protection against atherosclerosis (8).

A number of studies before 1975 demonstrated frequent hypercholesterolemia in diabetes. Much of this hypercholesterolemia, however, was likely due to previous dietary recommendations of low carbohydrate, and therefore, high fat and cholesterol diets. In a study involving children attending the Joslin Diabetes Camp (9), mean serum cholesterol was 20% lower in 1979 than in 1971. This was probably due to a change in dietary recommendations in the early 1970s from a diet containing 700–1500 mg/day of cholesterol and a ratio of polyunsaturated fat to saturated fat (P:S) of 0.1 to a diet containing 300–500 mg/day of cholesterol and a P:S ratio of 0.8–1.0.

Based on these data, it is appropriate to ask at this point how lipid abnormalities in diabetes could lead to accelerated atherosclerosis. In nondiabetic patients, the lipoprotein abnormalities that correlate best with coronary risk are elevated total or LDL cholesterol (10) and decreased HDL cholesterol (8). Although HDL cholesterol is somewhat diminished in non-insulin-dependent diabetic patients, it is normal or elevated in insulin-dependent diabetic patients. In addition, total and LDL cholesterol are not significantly elevated over values in the general population. Thus, from what lipoprotein abnormality does the increased risk for atherosclerosis come? To better understand this phenomenon, it is necessary to delve deeper into lipid pathophysiology in diabetes, because some abnormalities are not reflected in the lipid phenotype illustrated in Fig. 2.

Lipid Pathophysiology in Diabetes

Diabetes and Hypertriglyceridemia. As illustrated above, modest hypertriglyceridemia is common in diabetes. The magnitude of the triglyceride elevation increases in direct proportion with increasing fasting blood glucose or hemoglobin A_1C (11, 12). Nevertheless, one must be alert to inherited lipid abnormalities which are often exacerbated by the underlying diabetic state. Grossly lipemic serum due to fasting chylomicronemia is rarely due to diabetes alone and usually indicates a concomitant familial disorder (1).

Moderate fasting hypertriglyceridemia (triglyceride <800 mg%) is due to elevated VLDL. In most diabetic patients, this is due to a combined effect of increased VLDL production as well as decreased LPL-mediated catabolism (13). The predominant defect (increased production versus decreased removal) relates to the prevailing levels of insulin, glucose, and FFA (14). VLDL hypersecretion is the predominant defect seen in hyperinsulinemic, insulin-resistant states, such as obesity and impaired glucose tolerance. Insulin, in the presence of adequate FFA for substrate, stimulates hepatic VLDL synthesis and secretion. In hyperinsulinemic states that are not associated with insulin resistance (for example insulinoma) FFA levels are low, leading to a decreased availability of FFA substrate for hepatic triglyceride synthesis. Thus, peripheral insulin resistance is central to increased VLDL production by causing hyperinsulinemia and elevated FFA levels. The responsiveness of hepatic VLDL production to insulin is not as impaired by moderate insulin resistance as is glucose disposal in peripheral insulin target organs. Thus, hyperinsulinemia may produce only normal or subnormal glucose transport in peripheral tissues, yet stimulate VLDL production in the liver.

At the other end of the spectrum of hypertriglyceridemia is the insulin-deficient, thin, type 1 diabetic patient. Although FFA levels are high due to increased adipose lipolysis, the insulin deficiency keeps hepatic VLDL production low. However, LPL activity in adipose tissue and skeletal muscle is also very low. Thus, the primary etiology of hypertriglyceridemia in these patients is not increased VLDL production, but instead is decreased LPL-mediated VLDL clearance. The regulation of LPL is likely complex. However, LPL is clearly stimulated by an in vivo environment that includes insulin (induced by eating, or following an insulin-glucose infusion) (15, 16) and decreased in hypoinsulinemic states (as in poorly controlled insulin-dependent diabetes, and following a prolonged fast) (17, 18). In a recent study (19), the effect of insulin was assessed on LPL in primary cultures of human adipocytes. No effect of physiologic insulin concentrations was observed, suggesting that the in vivo effect of in-

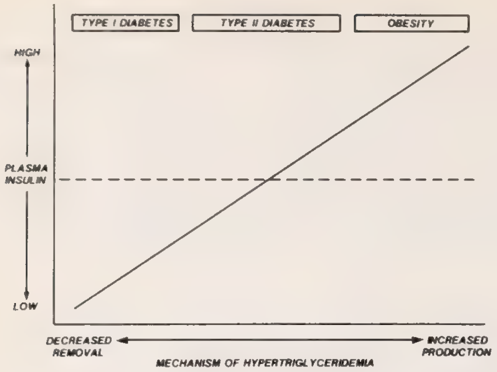

Fig. 3. Relationship between plasma insulin levels and mechanism of hypertriglyceridemia. Adapted from Bierman EL, Current concepts: hyperlipoproteinemia. 1984. *Reprinted with permission from the Upjohn Company.*

sulin to stimulate LPL functions through a second hormonal messenger or by increasing LPL at some other cell in adipose tissue.

In the non-insulin-dependent diabetic patient, both increased VLDL production and decreased LPL-mediated removal are usually present. Because FFA levels are normal or high due to peripheral insulin resistance and because the liver is reasonably well insulinized, VLDL production surges. On the other hand, clearance of VLDL via LPL is diminished (15, 20). Although the decreased LPL in non-insulin-dependent diabetes may relate to the insulin resistance, a recent study has implicated hyperglycemia per se as a cause of decreased adipocyte LPL (21).

These interactions between insulin, glucose, and FFA are illustrated in Fig. 3. Understanding the relative contributions of excessive VLDL production and decreased removal becomes useful in planning therapeutic regimens for hypertriglyceridemic diabetic patients, as discussed below.

Glucosylation of Lipoproteins and Collagen. Glucose has been shown to be nonenzymatically incorporated into proteins in proportion to the extent of hyperglycemia. Although glucosylated hemoglobin is the basis of a clinically useful measurement (hemoglobin A_1C), other proteins are also glucosylated and have altered function. Several recent studies have suggested that nonenzymatic glucosylation of lipoproteins may significantly alter their properties. When LDL is glucosylated in vitro (22), even to the extent found in diabetes (23), it is no longer degraded by the LDL (B-100:E) receptor as well as normal LDL. Because LDL is an atherogenic lipoprotein, a longer transit time in plasma may increase the overall risk for coronary artery disease.

A recent study has demonstrated that glucosylation of collagen yields products that bind LDL (24). The presence of glucosylated collagen may serve to make normal levels of LDL more atherogenic. Following endothelial injury, serum proteins (including lipoproteins) come into contact with the denuded vascular intima. Glucosylated collagen in the intima may trap LDL and thus promote the lipid accumulation that eventually leads to a fully developed atherosclerotic plaque.

Abnormal Lipoprotein Composition in Diabetes. Lipoproteins from diabetic patients have an abnormal composition not apparent on lipoprotein phenotyping. The hypertriglyceridemia of diabetes is characterized by a VLDL particle enriched not only in triglyceride but also in cholesterol (12, 25–27). Although this cholesterol-enriched VLDL is seen most consistently in non-insulin-dependent diabetes, it is also seen with poor metabolic control in insulin-dependent diabetes. The significance of cholesterol-enriched VLDL can be appreciated from studies on atherosclerosis in other systems. Monocyte-derived macrophages are important cells in the development of the atherosclerotic plaque. These cells enter the arterial intima as a result of endothelial injury and begin to accumulate lipid. Massive lipid accumulation often ensues, however, leading to transformation of the macrophage into a foam cell. Foam cells are found at the core of early lesions (fatty streaks) and are pathogenic of more advanced atherosclerotic plaques (28).

Hence, much effort has been devoted to understanding what types of lipoproteins stimulate lipid accumulation in macrophages. Macrophages contain few receptors for normal LDL and there is speculation that LDL must first be modified by endothelial cells or platelets before it can cause lipid accumulation in macrophages (29). However, macrophages contain specific receptors for a β-migrating, cholesterol-enriched form of VLDL (referred to as β-VLDL). This particle binds to macrophage β-VLDL receptors and stimulates massive lipid accumulation (30, 31). Hence, β-VLDL is an important atherogenic lipoprotein. Situations in which β-VLDL occurs naturally include patients with familial dysbetalipoproteinemia (Frederickson and Levy type 3 hyperlipoproteinemia) and following cholesterol feeding. Diabetic animals are especially prone to the development of cholesterol-enriched VLDL by cholesterol feeding (32). Although human diabetic

VLDL is cholesterol-enriched, it is not yet clear whether there is a significant amount of the specific β-migrating VLDL found in animals. However, in a recent study (27), VLDL isolated from normal subjects promoted some macrophage lipid accumulation, whereas cholesterol-enriched VLDL from both normolipidemic and hypertriglyceridemic diabetic patients stimulated a much greater lipid accumulation. This suggests that the abnormal composition of diabetic VLDL does indeed cause macrophage lipid accumulation, and thus may promote atherosclerosis.

Other abnormalities in lipid composition have also been described in diabetes. The ratio of apoprotein CII/CIII is reduced in diabetic patients (25, 33). Because apoprotein CII is an activator and CIII an inhibitor of LPL, a decreased CII/CIII ratio may explain part of the triglyceride removal defect. Another lipoprotein abnormality is triglyceride-enriched LDL (12, 34), which does not bind the LDL receptors as well as normal LDL (35) and which is found in increasing amounts in poorly controlled diabetes (12). Thus, numerous abnormalities in lipoprotein composition have been described in diabetes (Fig. 4), although the exact magnitude of their significance requires further study. Nevertheless, there is ample evidence that even subtle lipid abnormalities may predispose to the increased atherosclerosis of diabetes and thus suggests that these patients be treated aggressively.

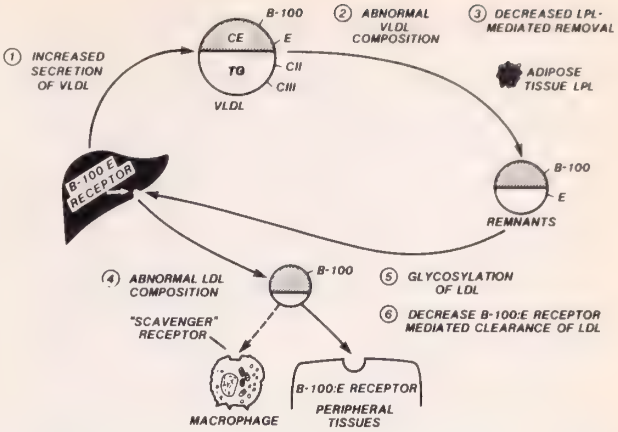
① INCREASED SECRETION OF VLDL
B-100
CE
E
TG
CII
CIII
VLDL
② ABNORMAL VLDL COMPOSITION
③ DECREASED LPL-MEDIATED REMOVAL
ADIPOSE TISSUE LPL
B-100
E
REMNANTS
B-100 E RECEPTOR
④ ABNORMAL LDL COMPOSITION
B-100
⑤ GLYCOSYLATION OF LDL
⑥ DECREASE B-100:E RECEPTOR MEDIATED CLEARANCE OF LDL
"SCAVENGER" RECEPTOR
MACROPHAGE
B-100:E RECEPTOR
PERIPHERAL TISSUES

Fig. 4. Potential sites of abnormal lipid metabolism in diabetes.

Treatment

The approach to the diabetic patient with hyperlipidemia encompasses two goals.

First, the chylomicronemia syndrome, with its attendant pancreatitis, mental confusion, and eruptive xanthomas, must be prevented. Patients are at risk for this syndrome when fasting plasma triglycerides exceed 1000 mg%. These patients essentially always have a familial form of hyperlipidemia in addition to diabetes as a cause of their disorder (1, 36).

The second goal of treatment is to reduce the risk of atherosclerosis. Firm data are not yet available to support any approach to reducing atherosclerotic risk in diabetic patients. Nevertheless, cardiovascular disease risk can probably be reduced significantly by diminishing the abnormalities described above, and hence are goals worth trying to achieve.

Among the most important features in the management of diabetic hyperlipidemia (Table) is good control of the patient's diabetes, which is essential and should be aggressively pursued. In insulin-dependent diabetes, this will usually involve a weight maintenance diet low in cholesterol and saturated fat, coupled with an insulin regimen that yields (near) euglycemia. For the non-insulin-dependent diabetic patient, diet and weight loss are of the utmost importance for lowering both lipid and blood glucose levels. In the process of following a low-cholesterol, low-saturated-fat diet, as defined in the Table, patients should be encouraged to eat several meals containing fish per week. The polyunsaturated oils in fish are rich in omega-3 fatty acids, which have an impressive lipid-lowering effect in nor-

TABLE

Treatment of Hyperlipidemia in Diabetes

1. **Diet**
   Goals: 20% fat, 65% carbohydrate, 15% protein, 100 mg cholesterol, polyunsaturated/saturated fats = 1.3. Abstain from alcohol if fasting chylomicronemia is present
2. **Weight loss**
   Goal: ideal body weight
3. **Metabolic control of diabetes**
   Goals for type 1 diabetic: as close to euglycemia as practicable with intensive insulin therapy
   Goals for type 2 diabetic: as close to euglycemia as practicable; diet and weight loss usually necessary before sulfonylureas or insulin are successful
4. **Drugs: indications, choices, dosage**

Triglyceride >400 mg%	**drugs of choice**	**maximum daily dose**
after optimizing diet,	gemfibrozil	1500 mg
weight, and metabolic	clofibrate	2000 mg
control of diabetes	nicotinic acid	7.5 gm
LDL cholesterol	cholestyramine	24 gm
>130 + age	nicotinic acid	7.5 gm
	lovastatin*	80 mg

* Not approved by the FDA as of February 1987.

mal as well as hypertriglyceridemic subjects (37, 38).

Oral Hypoglycemic Agents and Insulin. Further measures are usually needed to lower lipid levels in non-insulin-dependent diabetic patients. An attempt should be made to attain euglycemia with an oral agent, rather than with insulin, because some patients will attain lower triglyceride levels with a sulfonylurea than with insulin (39). This probably stems from the sensitivity of hepatic VLDL production to hyperinsulinemia in the presence of insulin resistance. An oral hypoglycemic agent will improve glycemic control by improving insulin sensitivity, and will not increase insulin levels (40). In contrast, large doses of insulin may attain euglycemia but hyperinsulinize the liver, and thus stimulate VLDL secretion. Nevertheless, adequate control of the diabetic state must be achieved. If oral agents plus diet prove inadequate to control hyperglycemia and hyperlipidemia, insulin must be used in spite of the potential problems with hyperinsulinemia.

If the patient remains hyperlipidemic, one of the drugs shown in the Table should be used. Gemfibrozil is particularly useful for the hypertriglyceridemia that is often seen; it is a well-tolerated drug that reduces triglyceride by 35%–50% and increases HDL cholesterol by about 20% (41, 42). This is accomplished by decreasing VLDL synthesis, increasing LPL levels (and thus increasing VLDL catabolism) and increasing HDL synthesis (42, 43). Clofibrate lowers plasma triglycerides to approximately the same degree as gemfibrozil but lacks the latter drug's beneficial effect on HDL. Nicotinic acid is also effective in lowering triglycerides, but its advantages can be outweighed by a drug-induced worsening of glycemic control (44, 45).

As discussed above, patients with diabetes do not have hypercholesterolemia solely because of their metabolic disorder. Thus, an isolated elevation in cholesterol would likely be due to an inherited lipid abnormality producing excessive LDL or IDL, such as familial hypercholesterolemia, familial combined hyperlipidemia, or familial dysbetalipoproteinemia (46 for review). Treatment should generally follow the same guidelines used for nondiabetic patients. Bile acid sequestants such as cholestyramine or colestipol enhance cholesterol excretion and thus lower LDL cholesterol. Drugs that are effective in combination with bile acid sequestrants include nicotinic acid and lovastatin (47, 48). Lovastatin appears to be particularly promising because it is an inhibitor of HMG-CoA reductase, the rate-limiting enzyme in cholesterol synthesis. In addition to blocking cholesterol synthesis, however, lovastatin causes an increase in LDL receptor activity in the liver as a counterregulatory response to decreased cholesterol availability (49). [Lovastatin had not been approved by the FDA as of February 1987.] The increase in LDL receptors helps to further lower LDL cholesterol in patients with an inadequate number of receptors (familial hypercholesterolemia).

Several caveats are worth mentioning concerning the above approach. For the patient with fasting chylomicronemia (triglyceride >1000), a familial disorder probably coexists. Hence, lipid levels in family members are helpful to delineate the nature of the disorder and to identify others at risk. Patients with fasting chylomicronemia should abstain from alcohol, which can raise triglyceride levels considerably. In obese patients, weight loss may be very effective in controlling hypertriglyceridemia; however, rapid weight loss should not be encouraged in patients with chylomicronemia. If a patient loses weight rapidly and then quickly regains the weight, the risk for pancreatitis and chylomicronemia syndrome is greatly increased (39). Hence, dietary therapy that aims at a gradual weight loss and a change in eating habits is most prudent.

Summary

Lipid metabolism in diabetes may be altered in a number of ways. Many patients manifest mild to moderate hypertriglyceridemia. In the presence of insulin deficiency, hypertriglyceridemia is usually due to a defect in VLDL removal, whereas in insulin-resistant states, there is usually a combined defect involving decreased removal and increased VLDL production. Severe hypertriglyceridemia occurs when the above defects are superimposed on a familial lipid disorder.

Other lipid abnormalities which are more subtle and not apparent in the lipid phenotype have recently been described in diabetes. Diabetic VLDL tends to be cholesterol-enriched, which may convert this triglyceride-rich lipoprotein into an atherogenic particle. LDL in diabetes becomes glucosylated and is triglyceride enriched, both of which impair receptor-mediated LDL clearance and probably increase the atherogenicity of LDL. Glucosylated collagen tends to bind LDL. Such a process may serve to trap LDL at sites of endothelial injury and promote formation of an atherosclerotic plaque. Further study is needed in these areas to determine the significance of these observations.

The goals of treatment are to reduce triglyceride levels to a point where pancreatitis is not a risk and secondarily to lower risk for atherosclerosis. Most of these goals can be attained by aggressively controlling the diabetes. All patients should consume a low-cholesterol, low-saturated-fat diet that is adjusted to the caloric needs of the individual. Insulin-dependent diabetic patients should receive intensive insulin therapy and non-insulin-dependent diabetic patients should be treated with diet, weight loss (if overweight), sulfonylurea drugs, or insulin as needed. If drug therapy is needed to lower triglycerides, gemfibrozil or clofibrate are the drugs with the greatest potential.

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Evaluation and Treatment of Diabetic Foot Problems

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The medical practitioner needs a sound approach to evaluate and treat the foot in diabetic patients. We often hear that minor trauma may quickly lead to ulceration, infection, gangrene, and amputation. Although this does occur, over the years we have been impressed by the large number of patients who either develop no lesions at all or have been walking on an open plantar ulcer for months or years and have not progressed to more severe complications despite the lack of local care. The challenge in our initial evaluation is to determine by history and examination which type of "diabetic foot" we are dealing with, so that we can more accurately predict the potential to develop complications. The goal of our treatment program is to prevent complications from occurring or, if complications have occurred, to resolve them and prevent future reoccurrences by directing treatment at the underlying cause.

The diabetic foot can potentially develop the same problems that nondiabetics experience. Clinical appreciation, however, is altered in the presence of vascular insufficiency or neuropathy, or both, when the potential for complications is far greater. A brief review of how angiopathy and neuropathy separately or together can lead to complication is important to better understand the essential aspects of the initial evaluation.

Neuropathy. Neuropathy may affect autonomic, sensory, and motor nerves. Loss of the autonomic nerves leads to diminished perspiration. The resulting dry skin can lead to cracks and fissures which are liable to infection. Sensory loss eliminates the patient's protective sensation, allowing trauma (mechanical or thermal) to go unnoticed. The patient with lack of pain stimulus does not automatically compensate in response to trauma, and this may in turn lead to ulceration. The ulceration may become infected, and this infection may progress to gangrene and subsequent amputation. Motor nerve loss leads to muscle atrophy and a progressive development of foot deformities. This creates new pressure areas that, when coupled with loss of protective sensation, may lead to ulcerations in areas that were previously not at risk.

Angiopathy. Angiopathy can be present as both large-vessel and small-vessel disease. Both the diabetic and nondiabetic population can suffer from the effects of large-vessel disease in which the flow of blood into the foot is reduced. The major difference is the possibility of extensive small-vessel disease and microangiopathy in the diabetic patient. Large-vessel disease can lead directly to gangrene by stenosis or occlusion. Large- and small-vessel disease together can produce an environment in which minor skin trauma leads to rapid and severe complications despite adequate care. Frequently, small-vessel disease may be advanced in comparison to large-vessel disease in the same patient. This explains the clinical appearance of vascular insufficiency in the presence of palpable pedal pulses.

Initial Examination and Working Diagnosis

The goal of our initial foot evaluation is to determine the risk category of our patients, potential areas where problems might develop, and —if a problem is present—to determine why it is present so that a definitive treatment program

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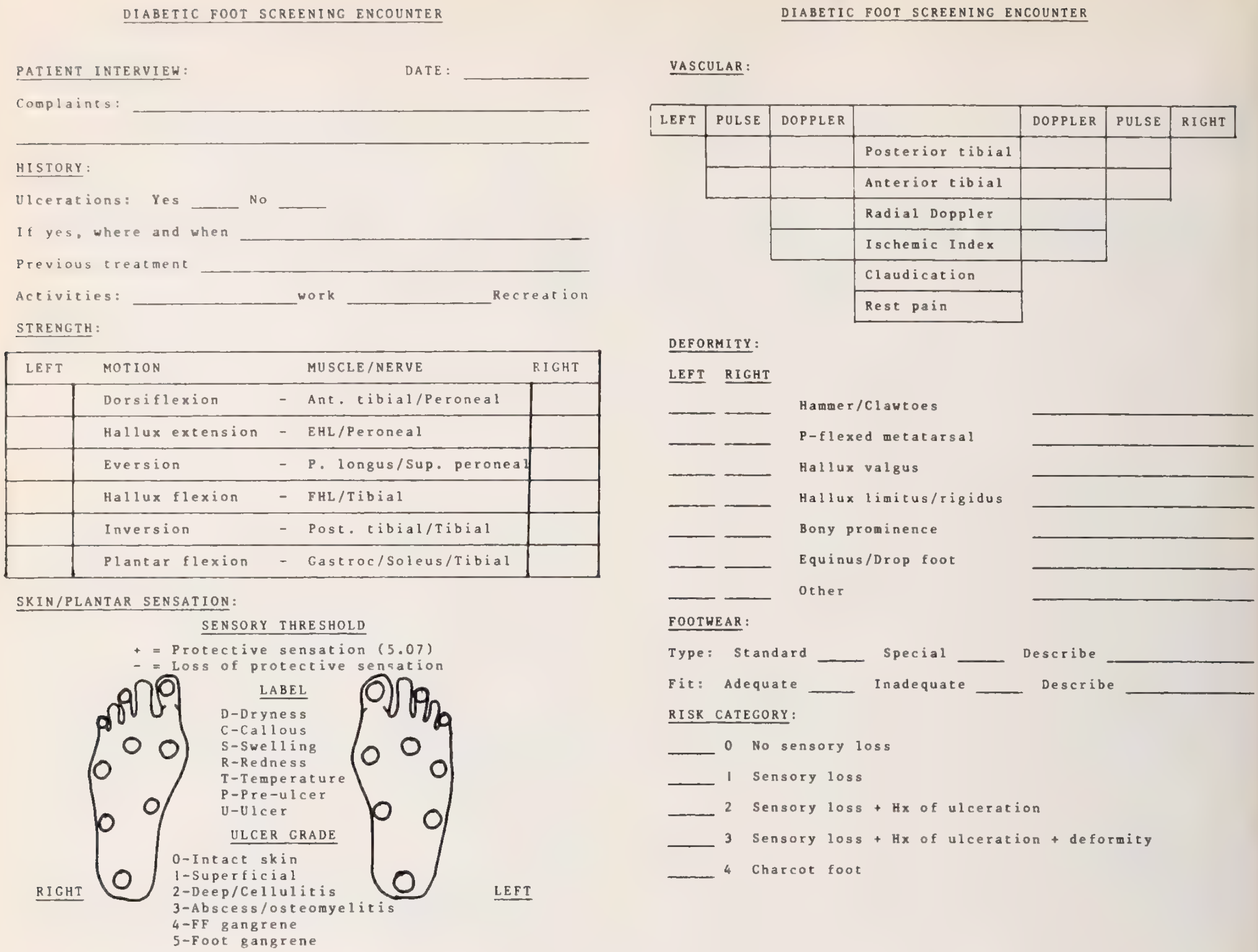


DIABETIC FOOT SCREENING ENCOUNTER

PATIENT INTERVIEW: DATE: ____________

Complaints: ______________________________

HISTORY:

Ulcerations: Yes _____ No _____

If yes, where and when ______________________

Previous treatment ______________________

Activities: ______________work ______________Recreation

STRENGTH:

LEFT	MOTION		MUSCLE/NERVE	RIGHT
	Dorsiflexion	-	Ant. tibial/Peroneal	
	Hallux extension	-	EHL/Peroneal	
	Eversion	-	P. longus/Sup. peroneal	
	Hallux flexion	-	FHL/Tibial	
	Inversion	-	Post. tibial/Tibial	
	Plantar flexion	-	Gastroc/Soleus/Tibial	

SKIN/PLANTAR SENSATION:

SENSORY THRESHOLD

+ = Protective sensation (5.07)
- = Loss of protective sensation

LABEL

D-Dryness
C-Callous
S-Swelling
R-Redness
T-Temperature
P-Pre-ulcer
U-Ulcer

ULCER GRADE

0-Intact skin
1-Superficial
2-Deep/Cellulitis
3-Abscess/osteomyelitis
4-FF gangrene
5-Foot gangrene

DIABETIC FOOT SCREENING ENCOUNTER

VASCULAR:

LEFT	PULSE	DOPPLER		DOPPLER	PULSE	RIGHT
			Posterior tibial			
			Anterior tibial			
			Radial Doppler			
			Ischemic Index			
			Claudication			
			Rest pain			

DEFORMITY:

LEFT RIGHT

_____ _____ Hammer/Clawtoes ______________
_____ _____ P-flexed metatarsal ______________
_____ _____ Hallux valgus ______________
_____ _____ Hallux limitus/rigidus ______________
_____ _____ Bony prominence ______________
_____ _____ Equinus/Drop foot ______________
_____ _____ Other ______________

FOOTWEAR:

Type: Standard _____ Special _____ Describe ______________

Fit: Adequate _____ Inadequate _____ Describe ______________

RISK CATEGORY:

_____ 0 No sensory loss
_____ 1 Sensory loss
_____ 2 Sensory loss + Hx of ulceration
_____ 3 Sensory loss + Hx of ulceration + deformity
_____ 4 Charcot foot

Fig. 1. Outline of initial examination leading to working diagnosis.

can be formulated. The diabetic foot examination is divided into four areas: dermatologic, musculoskeletal, neurologic, and vascular (Fig. 1). We hope to present an approach to foot screening which is concise, complete, and yet not excessively time consuming.

Dermatological Examination. The dermatological exam begins with an inspection of the foot and results in an overall impression of the patient's pedal condition.

A more detailed inspection is then initiated, beginning distally and proceeding proximally. Record each finding. Inspect the toenails, which may be hypertrophied, mycotic, or cryptotic. Often an ulceration may begin beneath a nail plate and go unnoticed until infection occurs. If the nail is loose or subungual hemorrhage is noted, suspect this possibility. If paronychia is present, check for ingrowing nail borders as a probable cause.

Look between the toes for fissures or mycotic involvement. In addition, note the presence of deformities and any hyperkeratotic lesions. A "corn" in the web space between the fourth and fifth toes may occur from friction and pressure between adjacent bones. In such an area, maceration occurs, and this is often mistaken for a mycotic infection. Differentiation is important because increased pressure from the lesion, coupled with weakening of the underlying tissue, may lead to ulceration and infection. Any area on the foot where a hyperkeratotic lesion is forming is a potential location for an ulceration if neuropathy develops.

It is common to misdiagnose a deep callus as a plantar wart. They appear to be similar on the surface because both will form a hyperkeratotic cover secondary to weight-bearing pressure. This cover must be debrided in order to determine the true pathology. A callus will demonstrate the presence of normal skin lines and will be located plantar to a weight-bearing bone. A wart is vascular and may be located anywhere on the foot. Normal skin lines will diverge around it, and capillary ends will be visible at its surface. This distinction is important because a callus is caused by excessive pressure, whereas a wart is caused by a viral infection. Their treatment will be quite different.

Always note which metatarsal head a plantar callus is located beneath. If the callus shows areas of hemorrhage, it is either preulcerous or an ulceration has already formed. This diagnosis cannot be made unless the callus is debrided. If an ulceration is present, its circumference and depth should be measured. Probe for deep pockets, and obtain specimens for gram stains and cultures. If deep tissues such as fascia, tendon, or bone are seen at the base of an ulcer, suspect that osteomyelitis is probably present even if radiographs are initially negative.

Various ulcer grading systems are discussed in the literature and are useful only if all practitioners at the same institution utilize the same system. One method we use to monitor the progress of ulcer healing is to make an exact tracing of the ulcer on a piece of exposed X-ray film. This is accurate and useful, particularly for other consultants treating the patient who may not be familiar with the progress of the lesion.

Musculoskeletal Examination. Any deformity that results in a bony prominence where either weight bearing or shoe pressure occurs is a potential area of ulceration in a neuropathic foot. These abnormalities most commonly include hallux abducto valgus, tailor's bunions, hammertoes, plantarflexed metatarsals, exostoses, or unusual deformities created by arthritis or charcot joints. Plantar hallux ulcers may be due to an interphalangeal joint sesamoid, a prominent exostosis, or to an often-overlooked hallux limitus or rigidus condition in which limitation of first metatarsophalangeal joint dorsiflexion during propulsion results in plantar pressure transfer to the interphalangeal joint level. This differentiation of causative factors may lead to significantly different treatment approaches to bring about the resolution of problems that occur in the same location.

Range-of-motion evaluation with muscle testing is necessary during the initial foot screening and will be important during treatment if special shoes, supports, or braces are necessary. Weight-bearing dorsal-plantar radiographs must be taken in the patient's angle and base of gait for standardization. In this way, functional musculoskeletal observations can be made which could not be appreciated on non-weight-bearing films. If any lesions are present, each one should be marked with metallic wire outlining its circumference so that weight-bearing films will demonstrate the relationship of the lesion to underlying bone. If no relationship is noted, the lesion may be due to a problem extrinsic to the foot (for example, a thumb tack in the patient's shoe).

Neurological Examination. The initial neurologic screening is essential but need not be extensive. The primary goal is to determine whether the patient has a minimum protective level of sensation. If this minimum level is not present, the patient will be at great risk for the development of ulcerations. A Semmes-Weinstein monofilament is utilized to test various areas of the foot (Fig. 1). Any patient who can feel the 5.07 filament has a minimum protective level of sensation. The monofilament will deform and exert only specified pressures, assuring test standardization. This simple examination will give immediate and important information that will later help to guide the treatment plan.

Vascular Examination. The screening is completed by evaluating the vascular status of the diabetic foot. At this point in the examination we have already made some observations which have given us an initial impression of the possibility of vascular compromise. The dorsalis pedis and posterior tibial pulses should now be palpated and graded. We are aware that diabetic feet with adequate circulation may exhibit weak or absent pulses or, conversely, vascular insufficiency may be seen in the presence of palpable pulses. Clinical experience increases the ability to recognize the effects of vascular disease; however, with the availability of the noninvasive Doppler examination, objective testing is possible.

To determine whether a full segmental Doppler with digital photoplethysmography should be performed by a vascular laboratory, an initial screening Doppler examination should be performed by the practitioner. A simple "pocket Doppler" can be utilized for the purpose of listening to the arteries and measuring the ankle:arm ratio (the ischemic index). The arm pressure is first measured using a standard blood pressure cuff with the Doppler over the radial artery. The ankle pressure is then measured in the same manner with an ankle cuff and the Doppler over the dorsalis pedis and posterior tibial arteries. The ankle pressure is divided by the arm pressure to give the ischemic index. A value of 1.0, indicating that the arm and ankle pressure are the same, would be considered "normal." A value less than 1.0 indicates some degree of vascular insufficiency is present. A value below 0.5 indicates that the patient has less than 50% blood flow to the foot and may not possess adequate tissue perfusion for healing. Referral to a vascular surgeon is essential in these cases even if no lesion is present. A value greater than 1.0 is a false positive and indicates calcified vessels that are not easily compressible by the cuff. A high value, or even a false positive, is still a good indicator of adequate healing potential when interpreted in the context of the total foot examination. The ischemic index, however, does not assist in the evaluation of microangiopathy which, although influential on healing, is less of a factor to consider when large-vessel competence is present.

Once the initial evaluation has been completed, a working diagnosis should be made, indicating both cause and effect. "Diabetic ulcer" is incomplete, and our needs may be better served by the diagnosis of "neuropathic diabetic ulcer secondary to a plantarflexed third metatarsal," which does address the cause and allows for the development of a more definitive treatment program.

Treatment

The goal of any effective treatment plan is to successfully resolve a problem. In the diabetic patient, it may sometimes be difficult to identify and sort out problems and underlying causative factors, but a goal-oriented treatment plan must be developed. Experience has taught us that in the diabetic, situations can deteriorate rapidly. A toe in jeopardy today may require a higher level amputation by tomorrow, and even the best intentions and "correct" treatment can end in disaster.

Management of specific problems in the diabetic population closely parallels treatment plans for the nondiabetic with similar conditions, except that we are dealing with a compromised host in the presence of an unforgiving systemic disease process. The purpose of this section is to assist the practitioner in establishing a logical treatment approach to foot problems that are prevalent among our diabetic patients. It aims to aid understanding a problem and determining a course of action to bring about the maximum restoration of function in as short a time as possible.

Patient Compliance. Many physicians have expressed frustration in dealing with diabetic foot problems because of inability to obtain patient compliance. Some understanding of why this occurs may be helpful. Patients with neuropathy have a body image that may extend only to their ankles. This is a psychologically depressing situation and leads to denial or underestimation of one's foot condition. As mentioned earlier, lack of a protective level of sensation allows foot trauma to go unnoticed, and the patient may not realize the existence of a neuropathic ulceration until very late into its progression. When examining a patient with pedal neuropathy, be sure to make physical contact with the patient in an area where your presence can be felt, such as a handshake, a touch on the arm, or a pat on the shoulder. This subtly relates that you are aware of the problem and understand the person's feelings in regard to his or her feet. This goes a long way toward establishing the rapport necessary to obtain enthusiastic compliance.

Education. The greatest positive impact that we, as practitioners, can provide is in the area of patient education. Hospital admissions for diabetic foot problems occur much more frequently among uninformed patients than among those who have been informed and instructed on the subject of diabetic foot care. Patient education is available in many formats and consists primarily of commonsense do's and don'ts. However basic this may seem, neglecting to disseminate this information may be a factor that leads to an amputation that could have been prevented.

Instructional materials are readily available at little or no cost from a variety of sources, including the American Podiatric Medical Association, the American Diabetes Association, pharmaceutical houses, and most hospitals.

Prophylactic Care. Although professional care of nails and skin conditions may be considered a luxury or a comfort measure among the general population, it is an absolute necessity for the patient with diabetes. Treatment may encompass reduction of nail plates, debridement of hyperkeratotic lesions, and instructing the patient in proper skin care and selection of shoe gear, and includes an ongoing monitoring of pedal status. Depending upon the exact nature of the problem, appropriate referrals may be required to provide the practitioner with the information necessary to resolve a specific situation. Multispecialty treatment is often necessary and may require consultations with podiatrists, vascular surgeons, orthopedic surgeons, plastic surgeons, radiologists, and infectious disease and diabetic specialists.

Nail Infections. Paronychia usually involves a specific nail border and is secondary to a cryptotic nail that has pierced the skin due to abnormal growth, improper trimming, or excessive shoe pressure. Management of an acute or chronic infection by warm soaks or oral antibiotics alone is not sufficient. The nail border is the causative factor, and, like a foreign body, must be eliminated to resolve the problem.

If the foot is neuropathic, no anesthesia is necessary, but usually we proceed as follows. The toe is blocked around the fleshy area of the proximal phalanx using approximately 2cc of lidocaine without epinephrine. The toe is scrubbed and painted with povidone-iodine solution. It is then exsanguinated and hemostasis maintained with a rubber band and hemostat. A small nail elevator is used to free the ungualabia completely from the nail edge. Using a nail nipper or English nail splitter, the nail border is cut back to the eponychium. Only the cryptotic edge need be removed. The nail is split back under the eponychium with a no. 62 blade (Fig. 2) and the nail edge gently avulsed with the nail elevator. The eponychium should not be excised, because incision creates unnecessary trauma and delays healing. The proximal nail fold is inspected for any nail spicules and the area checked for abscess pockets. Povidone-iodine ointment is applied followed by 2 × 2's and a mild compression dressing. Soaks are ordered for approximately three days. Partial avulsions usually demonstrate resolution of the infection rapidly without the need for oral antibiotics. When paronychia is encountered repetitively and there is evidence of adequate vascularity, a partial avulsion and chemical or surgical matrixectomy may be performed. This will allow for permanent correction of an ingrowing nail and reduce chances of recurrence and subsequent infection.

Hyperkeratoses. Hyperkeratotic lesions on the foot are a normal reaction of the skin to abnormalities in the distribution of pressure and friction. These lesions may be found superficial to any bony prominence or deformity and are influenced by the external presence of shoe gear or the support surface. The presence of hyperkeratotic buildups indicate areas that must, in the diabetic or neuropathic foot, be monitored and cared for carefully.

The causes of pressure must be identified and eliminated to prevent tissue breakdown and the subsequent deterioration to ulceration and infection. This may be done by debridgement of the lesion and protective skin padding or the fabrication of accommodative inserts or shoe gear.

It is absolutely imperative that the pressure source be removed, by external or internal means, or the problem will perpetuate and eventually progress toward complications.

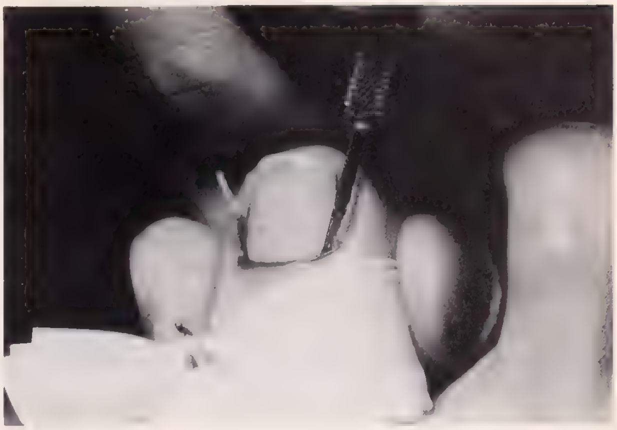


Fig. 2. Partial avulsion technique: nail is split proximally under eponychium prior to removal of ingrown border.

Digital Lesions. Hyperkeratotic lesions of the digits, often referred to as "corns," may be hard (heloma durum) or soft (heloma molle), depending on their location. Heloma durum formation is most commonly found over the heads of the proximal or intermediate phalanges secondary to contractures of the proximal or distal interphalangeal joints. These hammertoes may be flexible or rigid, depending on duration. Flexible deformities can be maintained in better alignment by the use of a traction-pad to reduce irritation from shoe pressure. More rigid deformities can be accommodated by aperture padding or shoe stretching. Padding placed directly over a pressure point will only serve to increase the pressure at that point and should be avoided. The frictional component of digital irritation may be reduced by having the patient apply a protective coating of petroleum jelly to keep the lesion slippery. This method does not take up space within the shoe toe box and is helpful in obtaining patient compliance.

Accommodation of digital deformities is difficult to accomplish and maintain without resorting to extra-depth shoes because the deformities tend to become more severe with time.

If the patient is in good diabetic control and demonstrates adequate tissue perfusion, the hammertoe deformity may be surgically corrected by soft-tissue releases or by conventional arthroplasty techniques at the appropriate levels. This will allow the patient to return to the use of conventional shoes and, more importantly, eliminate a potential source of future complications.

Heloma molle formation occurs between adjacent toes where the accumulation of moisture acts to soften the tissues. These problems tend to progress quickly, and ulceration can result if intervention is not prompt and definitive. After paring the lesion, an interdigital pad is fashioned to reduce pressure and maceration by maintaining separation of the digits. Again, surgical correction, if not contraindicated, may be utilized to correct the underlying osseous deformity.

If hyperkeratotic digital lesions are noted in nonconventional locations, suspect the presence of a bony prominence or exostosis as the underlying cause. Treatment is again directed at reduction of the pressure by whatever means are most applicable.

Plantar Keratomas. The "ideal" foot is designed to evenly distribute pressure across the metatarsal heads. In such a foot there would be no areas of focally increased pressure and, consequently, no reactive skin callus formation. The concept of the existence of a normal transverse metatarsal arch should be discarded. The existence of a hyperkeratotic plantar lesion should alert the practitioner to suspect an underlying biomechanical abnormality. In the diabetic foot, plantar calluses represent potential areas of ulceration, and treatment must be planned to promptly alter the pressure distribution if the foot is to be spared from the potential downward progression to ulceration, infection, and osteomyelitis.

Once the cause of the problem is known, treatment begins with debridement of the hyperkeratotic lesion. This is followed by attempts to externally raise or accommodate for the involved metatarsal or metatarsals utilizing jogging shoes, metatarsal pads, metatarsal bars, and functional or accommodative orthoses. Again, the use of petroleum jelly as a skin lubricant has proven to be an effective adjunct in the treatment and prevention of plantar keratomas.

Surgical correction of an elongated metatarsal may be performed by a shortening osteotomy utilizing internal fixation. Metatarsals that are plantarflexed may be corrected by dorsal wedge osteotomies at the metatarsal base or by tilt-up or elevating osteotomies at the metatarsal neck.

Osteotomies of the lesser metatarsals have the inherent complication of transfer lesion production. Utilization of these procedures should therefore be reserved for situations in which accommodations are not sufficient to prevent recurrence. Metatarsal osteotomy is, however, preferable to metatarsal head resection.

Recently, two nonsurgical modalities have been evaluated as alternative means of dealing with plantar pressure inequality. Fluid silicone augmentation and collagen implantation allow for the creation of an internal cushion between the metatarsal head and the skin. Neither is available for use in the diabetic patient at this time, but initial investigations seem to demonstrate significant promise.

Plantar Ulcerations. Ulcers in the diabetic foot are the consequence of focally increased pressure areas and may often be the end result of inadequately treated plantar keratomas. For the diabetic foot specialist, ulcers are a clinical challenge and require implementation of the sum total of our experience, judgment, and skills.

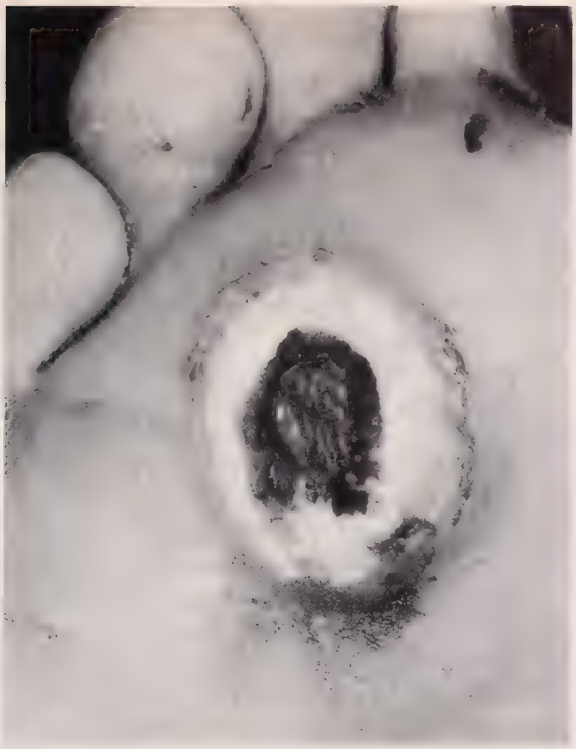
The progression from plantar keratoma to ulceration usually takes place in a situation of coexisting diabetic neuropathy. The absence of a protective level of sensation allows for painless soft-tissue destruction without the patient's ability to compensate. This pathway of deformity, pressure, neuropathy, and ulceration is similar to that occurring in patients with Hansen's disease. The diabetic patient, however, has to contend with the systemic interplay of hyperglycemia and vascular disease in addition to neuropathy, resulting in foot ulcers that are more complex to treat than those in the patient with Hansen's disease alone.

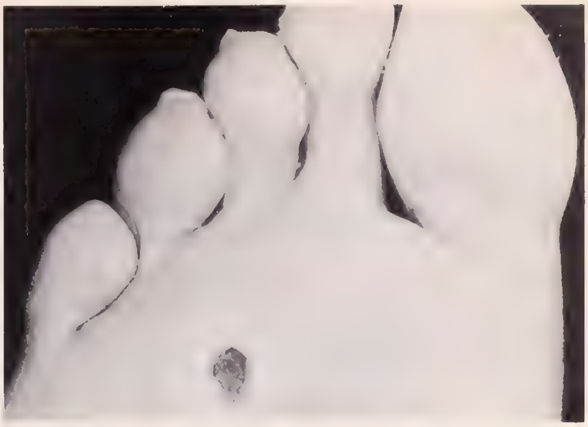
The ulceration is first carefully evaluated and debrided. If an abscess pocket is noted, it must be incised as wide as it is deep. A definitive diagnosis may now be established (neuropathic diabetic ulceration secondary to a plantarflexed metatarsal).

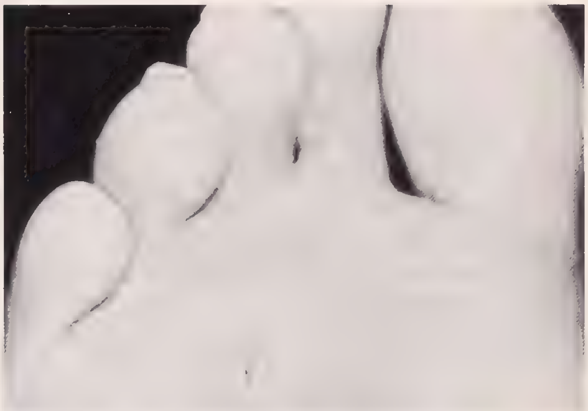
Vascular assessment will delineate the healing potential of the area. Ulcerations in patients with less than 50% blood flow to the foot may not have adequate circulation to heal or to deliver appropriate levels of antibiotics. For such patients, referral to a vascular surgeon for evaluation and possible bypass grafting may represent the first step in treatment.

If adequate healing potential exists, the next step is to decide how to reduce the plantar pressure enough to allow healing to begin. This is the key to successful ulcer treatment.

We have all heard various clinicians discuss the benefits of different medications and dressings, but the ulceration will progress and heal normally only in the absence of plantar pressure, regardless of the form of dressing. Experience has shown that in the presence of adequate circulation, enforced bedrest will allow most ulcers to heal. This may, however, be dele-







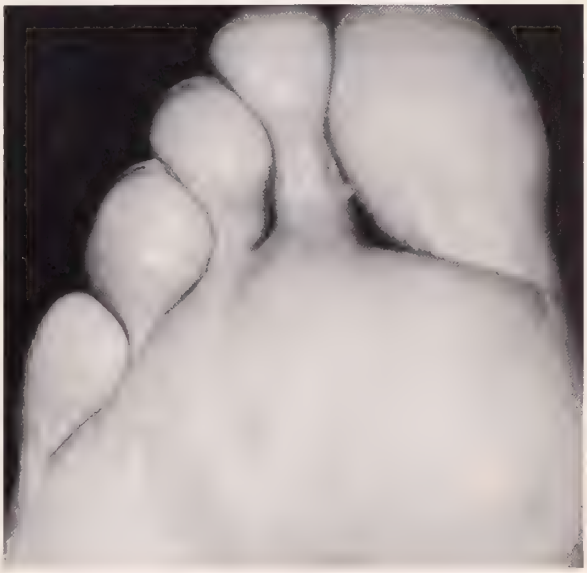


Fig. 3. Patient with nonhealing ulceration of 18 months' duration. **Above** Initial presentation after debridement.
Fig. 4. **Top right** Ulceration after two weeks of total contact plaster casting.
Fig. 5. **Middle** Ulceration after third week of total-contact plaster casting. Complete healing was noted following fourth week of treatment.
Fig. 6. **Bottom** Ulceration remains closed one year after treatment. An accommodative device has been utilized in conventional shoe gear.

terious to the patient's overall health and has become prohibitively expensive. Non-weight-bearing crutch-assisted ambulation is an alternative for unilateral conditions if the patient is physically able to comply. These are the only methods of obtaining 100% pressure reduction.

When treating ulcers in ambulatory patients, our goal is to achieve sufficient reduction in plantar pressure to allow healing to occur. This may be accomplished by the use of pads, moldable footbeds, or other accommodative devices. In refractory conditions, we have used the total-contact plaster cast (TCPC) principles and techniques that have proven effective for so many years in the treatment of relatively uncomplicated neuropathic ulcers in patients with Hansen's disease. The application and removal of these casts is both time-consuming and tedious, requiring extreme care. Once learned, the TCPC is a valuable out-patient alternative to complete bed rest, improves patient compliance, and has become an indispensible part of our treatment program for ulcers resistant to management with accommodative devices.

Total-contact casts distribute plantar pressure over as large a surface area as possible and can reduce focal pressure by as much as 85%. Fear of ulcer enclosure is initially difficult to overcome, but the ulcer will heal regardless of how often it is observed. Use of the TCPC is contraindicated in the presence of anaerobic infections, profuse drainage, fever, cellulitis, vascular insufficiency, or severe edema, or when the patient is totally noncompliant.

We usually begin cast treatment with a soft unna-boot to reduce edema for two to three days prior to application of the TCPC. This is important because the initial TCPC will reduce swelling very quickly, allowing pistoning and the subsequent creation of new pressure ulcers. The TCPC is usually applied for one week intervals. Following each cast removal, the ulcer is again debrided, measured, and dressed with a gauze pad soaked in povidone-iodine solution. Casting is continued until healing is completed, and impressions of the feet are taken for the fabrication of accommodative orthoses for use during the posthealing period (Figs. 3–6). If the patient returns to full activity and the ulceration remains healed, no additional treatment is required other than periodic monitoring. Recurrence of the ulcer despite accommodations indicates a need to consider surgical intervention for correction of the underlying causative factors.

Complicated ulcers exist with concomitant infection of the deeper soft tissues and bone and are not to be initially managed by casting. Patients afflicted with ulcers of this type usually require hospitalization, parenteral antibiotics, bedrest, and/or surgical debridement of osteomyelitis. Radiographic diagnosis of osteomyelitis usually cannot be made early, and valuable time may be lost waiting for a film to demonstrate bone destruction. If we encounter joint fluid or note deep necrotic tissue (capsule, tendon, bone, or ligaments), it is best to presume the presence of osteomyelitis and proceed accordingly.

Surgical Philosophy. Surgical correction of many musculoskeletal foot deformities in nondiabetic persons has historically been elective and reserved for those conditions which are chronically painful or result in severe difficulty fitting or putting on shoes. The diabetic patient, however, must be considered from a different perspective.

Many of us have been instructed during our education and training not to operate on diabetic feet. However, we are often called on to perform ablative salvage procedures when risk factors are high, as in osteomyelitis, soft-tissue infections, or gangrene. If adequate vascularity is present, the surgical wound will usually heal. These procedures generally result in the creation of a weight-bearing extremity that is more prone to the development of additional complications due to abnormal pressure distribution. It is more prudent to operate when the risk factors are low and to correct the causes of the problems rather than waiting for complications to occur. It is better to correct a hammertoe now than to wait until shoe pressure on the deformity leads to chronic ulceration, osteomyelitis, and gangrene, thus requiring digital amputation.

If, in our best judgment, we feel that the deformity, if left untreated, will progress toward complication, then surgical intervention may be considered a conservative treatment of choice.

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Management of Diabetes Mellitus in Pregnancy

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It is estimated that 5% of the population now have overt diabetes mellitus. The causes for this increase are not known but environmental factors as well as genetic predisposition are implicated. About 4–5 per 1000 pregnancies involve a mother with insulin-dependent diabetes. However, glucose intolerance develops during pregnancy (gestational diabetes) in approximately 3%–12% of the general pregnant population who are nondiabetic at the time of conception (1). This glucose intolerance contributes to a twofold increase in perinatal mortality and increased maternal and neonatal morbidity. Moreover, there is a 2–3–fold increase in the incidence of congenital malformations in the neonate, many of which are lethal (2). Perinatal mortality in glucose-intolerant pregnant women has decreased markedly over the past 25 years; from more than 10% to well under 4% in most recent reports (3–6). In many centers which use a multidisciplinary approach the perinatal mortality rate in glucose-intolerant pregnant women does not markedly differ from their non-glucose-intolerant pregnant population.

Pathophysiology. Pregnancy is a "diabetogenic state," that is, a normal pregnant woman is required to produce and secrete more insulin as pregnancy progresses to maintain euglycemia. This pregnancy effect is primarily thought to be due to placental hormonal insulin antagonism, particularly human placental lactogen (HPL), which exerts physiologic effects opposite from insulin. Increasing levels of progesterone, estrogen, cortisol, and placental insulinase have also been implicated as factors resulting in the increased risk of glucose intolerance with advancing gestation.

Those patients who have preexisting diabetes mellitus similarly note a substantial increase in their insulin requirements during pregnancy, particularly in the second and third trimesters, to maintain a level of glucose control comparable to their nonpregnant state. Most frequently, a combination of both intermediate-acting (NPH, lente) and short-acting (regular) insulin given as two separate injections in the morning and evening is required to obtain satisfactory glucose control. Large amounts of insulin are frequently required to achieve adequate glucose control, particularly in obese pregnant patients, whose insulin resistance may be marked.

Screening and Diagnosis. Every pregnant patient should probably be screened for glucose intolerance during gestation. If this cannot be done, health care professionals must be knowledgeable of the risk factors particularly relevant to the development of glucose intolerance during pregnancy. Those risk factors in the mother's family and previous obstetric history which have been implicated include:

1. Maternal age of 25 years or more.
2. A previous diagnosis of gestational diabetes.
3. Family history of a first-degree relative (parent, sibling, or child) with diabetes.
4. Obesity.
5. A previous infant with a birth weight greater than 4000 gm or 9 lb.
6. A previous stillbirth.
7. A previous infant with major congenital anomalies.
8. Habitual abortions.

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Risk factors that develop during a current pregnancy that indicate that glucose intolerance may be present include:

1. Uterine size greater than the patient's gestational date.
2. Ultrasonic evidence of fetal macrosomia or hydramnios.
3. Developing glycosuria.

Various screening tests have evolved to identify and define the degree of glucose intolerance during pregnancy. Whether all pregnant women or only women with known risk factors are screened for glucose intolerance, a standard screening regimen should be used. Many such regimens have been advocated, but we strongly support the use of 1-hr plasma glucose obtained after the oral ingestion of 50 gm of glucose. This screening test is performed without special preparation and without regard to time of last meal or time of day. The initial screening test is best timed at approximately 24–28 weeks of gestation. A plasma value greater than or equal to 135 mg/dL is considered abnormal, and the patient is then instructed to have a full 3-hr glucose tolerance test (11).

Many different interpretation regimens have been advocated for the 3-hr glucose tolerance test. If a glucose tolerance test is necessary, the patient must fast for the previous 8–14 hr and precede the test with at least 3 days of unrestricted diet in which more than 150 gm of carbohydrate is ingested per day. We use plasma values of 105 mg/dL fasting, 190 mg/dL at 1 hr, 165 mg/dL at 2 hr, and 145 mg/dL at 3 hr as the normal levels for plasma glucose determinations for interpretation of the 3-hr glucose tolerance test (11, 12). A patient is considered to have abnormal glucose tolerance during pregnancy when any two of these values are abnormal or if there is an abnormal fasting blood sugar.

Classification. The most widely utilized classification system was originally developed by Priscilla White. This system is based upon age of onset of diabetes, its duration, and degree of vasculopathy. We currently use a modification of the White classification system (13) as follows:

Class A-1: gestational diabetes with normal fasting plasma glucose.
Class A-2: gestational diabetes requiring insulin therapy.
Class B: insulin-requiring (onset of use at greater than or equal to 20 years old) and duration less than 10 years. No vascular complications.
Class C-1: age 10–19 years at onset.
Class C-2: duration 10–19 years.
Class D-2: over 20 years' duration.
Class D-3: benign retinopathy.
Class D-4: calcified vascularity of lower extremities.
Class D-5: hypertension.
Class F: nephropathy.
Class H: cardiomyopathy.
Class R: proliferative retinopathy.
Class T: renal transplantation.

Although this classification system allows easy placement of each patient in a particularly relevant group and has prognostic significance, current management has considerably narrowed the perinatal outcome in all of these classifications so dramatically that the practical value of such a classification system is somewhat limited. It is probably much more relevant to assess the individual maternal metabolic status and the vascular and organ involvement to determine the effect upon maternal and neonatal outcome. Clearly the compounding factors of ketoacidosis, infection, hypertension, and poor patient compliance are more often associated with unfavorable outcomes.

Management of Diabetes Diagnosed Before Pregnancy

Prepregnancy Evaluation. Congenital anomalies are found 3–4 times more frequently in infants of overtly diabetic women than in offspring of nondiabetic women. Factors that have been implicated in the etiology of malformations in infants in diabetic mothers include genetic influences, teratogenic drugs, and metabolic disorders. The inheritance of glucose intolerance is complex and not well understood, thus making it difficult to assess the influence of genes on congenital malformations in infants of diabetic mothers. It is clear that there is not a simple explanation, since a number of investigators have shown that the prevalence of congenital anomalies is significantly higher in infants of diabetic mothers than in infants of diabetic fathers (8). In fact, the frequency of malformations in infants of diabetic fathers is not significantly different from that of infants of nondiabetic fathers. In addition, the absence of reports of the recurrence of identical abnormalities in subsequent pregnancies does not support a pure genetic mechanism. Drugs have been suggested as potential teratogens in infants of diabetic mothers and include insulin and oral hypoglycemic agents. The period during which the conceptus is most susceptible to the effects of the teratogenic agent is the period of organogenesis, approximately the second to the eighth postconception weeks. It is during this period that the major malformations seen in infants of diabetic mothers occur (14). Maternal insulin does not cross the placenta and fetal insulin production does not appear to begin until after the eighth postconception week. These observations suggest that insulin probably does not directly cause these associated anomalies. Moreover, most studies involving oral hypoglycemic agents have not shown an increased incidence of *major* congenital anomalies.

The majority of the evidence implicates metabolic disturbances (specifically, hyperglycemia) during organogenesis as the primary cause of anomalies in infants of diabetic mothers. The specific mechanism involved has not been elucidated. Improvements in first-trimester glycemic control have been associated with a lower prevalence of congenital malformations (7). In order to reduce the prevalence of congenital anomalies among infants of diabetic mothers, it is necessary to institute strict metabolic control prior to conception, to diagnose pregnancy as early as possible, and to maintain as nearly normal glycemic levels throughout organogenesis as possible. Unfortunately, many diabetic women are not aware of the association between poor metabolic control during the period of conception and the associated risk for congenital malformations. Prepregnancy patient education raises the patient's awareness of their increased risk for anomalies with poor control. It has been shown that the overwhelming majority of patients counseled before pregnancy were able to maintain strict metabolic control during this first trimester when compared to patients who sought counseling after pregnancy had been diagnosed (9).

Glycosylated hemoglobin, or hemoglobin AlC (HGB AlC), as a percentage of total hemoglobin A is a useful measure of the patient's glycemic control during the 2–3 months preceding pregnancy. It has been shown that there is a substantial increase in the prevalence of major anomalies among infants of diabetic mothers who had elevated first-trimester hemoglobin AlC levels (7). In contrast, the prevalence of major congenital anomalies is similar to the nondiabetic population when the hemoglobin AlC level is near normal during the first trimester. Therefore, patients with overt diabetes in pregnancy should have a first-trimester hemoglobin AlC determination. If this hemoglobin AlC value is substantially elevated, the patient should receive detailed counseling on the risk for major fetal anomalies. If the patient chooses to continue the pregnancy, she should be followed up with a serum alphafetoprotein determination and a detailed and systematic (level II) ultrasound examination between 16 and 20 weeks of gestation. These examinations are particularly important in the detection of the major associated anomalies, which include neural tube abnormalities and cardiac, renal, and skeletal malformations, at a time when intervention can still be considered.

Nutritional Management. The goal of nutritional management is to individualize care to meet the nutritional needs of the mother and fetus and support appropriate weight gain while maintaining optimal blood sugar control. Recommendations for nutritional support for pregnant women with diabetes follow the same daily dietary allowances for nutrients used for the nondiabetic pregnant woman.

To meet desired weight gain goals for optimal perinatal outcome, normal-weight women should be encouraged to gain approximately 24–27 lb, underweight women a minimum of 30 lb, and overweight women 15–24 lb. The pattern of weight gain is probably more significant than the absolute amount of weight gained; the desired pattern is approximately 3–4 lb in the first trimester and approximately 0.9 lb per week in the second and third trimester.

Strict attention should be paid to individualizing calories for each patient to support appropriate weight gain. When estimating appropriate calorie levels, the clinician should take into consideration the patient's prepregnancy weight status, caloric needs, age, activity level, current intake, total weight gain, and pattern of gain. The simplest way to assess adequacy of the calorie level prescribed is to evaluate diet compliance and the pattern of weight gain. In general, most patients, including obese patients, gain weight appropriately when their caloric consumption is in the range of 1,800–2,600 calories per day.

The diet plan should take into account the pregnant diabetic's food preferences, lifestyle, and need for insulin. Gestational diabetics benefit from a minimum of three meals and a bedtime snack to prevent nocturnal hypoglycemia. For women on insulin, the distribution of food into meals and snacks will depend on the type of insulin, activity level, and patient's own experience with her blood sugar control. In early pregnancy, small frequent meals and snacks may be helpful in preventing hypoglycemia and treating the frequent problem of associated nausea. Most women receiving 2 injections daily of NPH and regular insulin do well with 3 meals and 2–3 snacks per day. Meals are planned with an even distribution of carbohydrates, protein, and fats within the overall goal of providing 45%–60% of calories from carbohydrates, 12%–20% from protein, and 20%–35% from fat (10).

In addition, consider optimizing water-soluble fiber and complex carbohydrate intake; both appear to have a positive effect in controling postprandial blood sugars. Water-soluble fibers have the added benefit of decreasing serum cholesterol. This particular dietary management, which emphasizes specific foods for their glycemic-controling effects, may be particularly helpful for patients with borderline glucose intolerance (15).

Use of alcohol and products containing caffeine, saccharin, and aspartame should be reviewed with the patient. Abstinence from alcohol is the safest recommendation for fetal development and for the prevention of unnecessary hypoglycemia, due to alcohol's inhibiting effect on gluconeogenesis in the liver. The nutrition plan for the pregnant diabetic is not complete unless it includes goals for nutritional care of the mother and baby after delivery. Diets should be planned to promote a gradual return to ideal body weight, and mothers should be encouraged and supported in breast-feeding their babies.

Metabolic Control. Glucose control must be monitored regularly throughout pregnancy. This can best be achieved by the patient at home using either glucose oxidase reagent strips with a color chart or the regular use of a glucose reflectance meter. Patients can then assess their level of control in their usual environment following their regular dietary and exercise regimens. Glucose control should be assessed regularly in the fasting state and before each meal. Postprandial determinations may also be required. In general, the maternal plasma glucose levels sought are fasting level 60–90 mg/dL; postprandial level 120 mg/dL. Hypoglycemia and maternal ketonuria should be avoided.

Probably the single most important factor for successful management of pregnant diabetics is compliance with home glucose monitoring. We now know that the blood glucose levels have implications for the mother's long-term complications as well as for neonatal mortality and morbidity. Daily information on blood glucose levels is necessary for appropriate management and as a means of giving the patient more control and participation in her care.

Many systems of home glucose monitoring are available today. Two methods exist for interpreting capillary blood glucose: visual inspection and the use of a meter. In pregnancy when insulin management is required, the glucose meter is preferred for home evaluation of plasma glucose; it is more precise and accurate and gives exact numbers instead of a range of values. Non-insulin-dependent diabetics may use visual systems with guidelines to aid in their management. The frequency of capillary glucose testing depends on the management plan. Diet-controlled patients may be asked to test their plasma glucose once or twice a day. Other patients on complex insulin regimens may be required to test their plasma glucose up to 8 times a day. The majority of patients require assessment approximately 4 times a day. The nurse can play an essential role in coordinating this activity and providing liaison between the home and ambulatory health-care environments.

Patients taking insulin should have regular contact with their health-care team weekly. Fetal evaluation, including antepartum surveillance, should begin no later than 34 weeks' gestation. If intrauterine growth retardation is suspected, testing may need to begin earlier. Serial ultrasound exams for adequacy of fetal interval growth is essential. The goal of this type of surveillance is to allow the health-care provider to delay delivery safely until the fetus has gained sufficient maturity.

Liberal hospitalization remains an important part of treatment for patients with poor glucose control throughout pregnancy or who have other medical complications. Most patients have a satisfactory outcome and are readily able to achieve a good glucose control without hospitalization. The timing of delivery should depend on a combination of maternal and fetal factors. In general, those patients requiring insulin throughout pregnancy will have an elective delivery after fetal pulmonary maturity has been established. Some patients who have a completely uncomplicated course may be expectantly followed until spontaneous labor occurs and deliver at term. Because of the care needed in managing maternal glucose control and because of potential neonatal morbidity, it is particularly important that the delivery be performed at an institution with levels of maternal and neonatal care skills commensurate with the risks.

The standard test used for assessing fetal pulmonary maturity is the amniotic fluid phospholipid profile. A combination of the lecithin/sphingomyelin ratio and an assessment of the presence of phosphatidyl glycerol are utilized. For management of maternal glucose levels during labor, we prefer to use a continuous intravenous infusion of both insulin and glucose. The amount of insulin is titrated to the plasma glucose values, which are determined every 1–2 hours.

Gestational Glucose Intolerance Only. When the diagnosis of gestational diabetes has been made, the patient is placed on an appropriate diet prescribed to maintain normal weight gain. This is a diet recommended by the American Dietetic Association and excludes simple sugars. The patients are seen every two weeks until week 33–34. Fasting and postprandial plasma glucose levels are evaluated at each appointment. If the fasting glucose remains below 105 mg/dL and the postprandial values remain below 120 mg/dL, continued dietary management is carried out. In those patients exceeding these levels, insulin therapy is considered. Antepartum fetal surveillance is performed beginning at 34–36 weeks in patients who have associated complications, including macrosomia, hypertension, or previous stillborn. In general, these patients are followed until term and spontaneous labor is awaited. For those patients going beyond their estimated date of confinement, serial twice-weekly fetal assessment is performed and if the cervix is favorable, induction of labor is indicated.

Postpartum Care. Diabetic patients continue to require special attention after delivery. In general, those patients who had been on prepregnancy insulin will require readjustment of their insulin dosage. The amount of insulin is determined by serial blood-glucose monitoring. Insulin requirements usually substantially decrease to up to 50% of the prepregnancy requirement in the initial postpartum days. Hypoglycemia and insulin reactions should be carefully observed for. Breast-feeding is not contraindicated for the diabetic mother and should be encouraged. Family planning needs should be reviewed and the risk of diabetes and the various contraceptive methods assessed for each patient.

Nursing Management. Nurses can provide education and guidance from preconception to postpartum. Adequate patient education is a major factor in the successful outcome of these complicated pregnancies. Nurse educators assess the patient's skill level, level of understanding, and motivation to decide on an educational program for each patient. The major areas of education include instructing the patient in (1) home glucose monitoring and recording of blood glucose measurements, (2) insulin preparation, administration, and rotating of injection sites, and (3) urine testing for ketones, as well as (4) reviewing dietary counseling, (5) reinforcing the importance of good glucose control, and (6) providing support and general overall counseling.

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Infants of Diabetic Mothers: Prenatal Care and Outcomes for the Infant

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Pregnancy for the diabetic woman is now more often associated with a normal outcome than in the past, a change attributable in part to our greater understanding of the cause of many diabetes-associated prenatal disorders and in part to our ability to provide better care for these women during their pregnancies. The purpose of this article is to describe the underlying basis for the ideal care for the diabetic pregnant woman, as well as the outcome as reflected in the state of the infant born in such pregnancies.

First, I summarize current theories on the pathogenesis of the disorders commonly seen in offspring of diabetic pregnancies. To do so it is necessary to distinguish between those disorders which arise as a result of difficulties during organogenesis (structural disorders) and those which occur late in pregnancy (functional or biochemical disorders) (Table). A further distinction has been attempted between disorders which occur in offspring of known, insulin-dependent (type 1) diabetics and in offspring of those whose diabetes is recognized only during pregnancy ("gestational" diabetics). Types of diabetes in pregnancy are completely described by Oakes et al in this issue.

Second, I describe the means of diagnosis, performed either prenatally or immediately after birth, for several disorders in these infants. Finally, I devote attention to treatment directed at minimizing postnatal sequelae.

Pathogenesis of Disorders in Infants of Diabetic Mothers

The term "congenital anomaly" encompasses both structural abnormalities—malformations present at birth and recognizable by the physical examination (1)—and functional problems which have their origin in the perinatal period and are detrimental to the physical well-being of the newborn. In the latter category are such disorders as macrosomia, hypoglycemia, and hyperbilirubinemia. It is possible to distinguish these abnormalities by the period of gestation during which they develop (2).

Structural Disorders: Developmental Hypotheses. The major structural abnormalities which have been associated with diabetic pregnancies include skeletal abnormalities, such as sacral agenesis or absence of the femur; genital abnormalities, including cryptorchidism and hypospadias; cardiac abnormalities, including ventricular septal defect and pulmonary artery stenosis; and gastrointestinal tract abnormalities, including gastroschisis (3–6). As pointed out by Mills et al. (6), these disorders occur in the embryonic stage of organ and skeletal development, completed in the human fetus by the eighth week following implantation. Thus, the presence of structural malformations indicates a disturbance in the normal developmental process which must occur prior to the eighth week of gestation, well before the end of the first trimester of pregnancy (6).

A theory to explain the development of the structural disorders which occur in diabetic pregnancy has emerged from the work of Deuchar (7),

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and more recently from Freinkel et al. (8). As was originally shown in tissue culture studies of rat embryos, Deuchar (7) was able to induce many of the midline defects occurring in offspring of diabetics by introducing serum from pregnant diabetics to the culture medium. The identity of substances present in the serum which induce these abnormalities was not determined.

More recently, work from Freinkel and his group (8), employing rat embryos in culture, has shown that introduction of mannose to the culture medium at extremely low concentrations (1.5 mg/ml) was sufficient to produce neural-tube and other midline defects simultaneously with an inhibition of glycolysis, leading to the concept of "fuel-mediated" teratogenesis (Fig. 1). These experiments were based on the finding that mannose is lethal to the honeybee, an organism highly dependent on glycolysis for energy production. The data indicate that organogenesis is highly sensitive to changes in glycolytic flux, since the effects of mannose could be offset by the addition of increased glucose or oxygen (8).

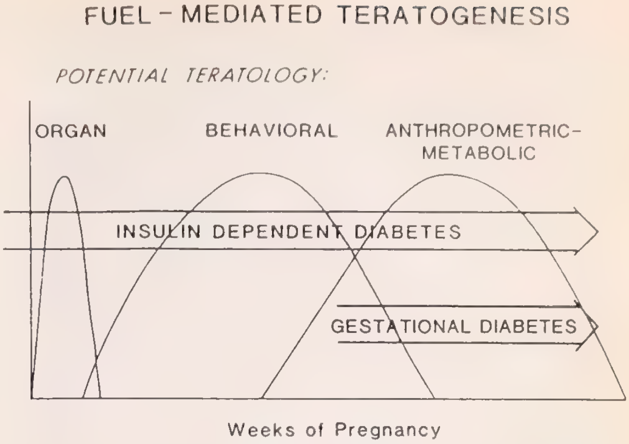

Fig. 1. Graphic representation of effects of disturbed maternal carbohydrate metabolism on process of fetal development during various stages of pregnancy. *Reproduced with permission from American Diabetes Association (45)*

It has been suggested that increased levels of maternal glycosylated hemoglobin (Hgb A_1C), seen in poorly controlled diabetes, could result in impairment of oxygen delivery (9). One could speculate that reduction of oxygen delivery to the fetus in this way might well cause the structural anomalies described above. This is supported by the observation that careful diabetic control in the prenatal period, by means of subcutaneous insulin infusion in a group of insulin-dependent diabetic women, was associated with a reduction in the rate of structural congenital anomalies (10). Women treated in this way had levels of Hgb A_1C comparable to normal prior to conception.

TABLE

Potential Disorders in the Infant of the Diabetic Mother

Structural	Functional
Prior to 8th week gestation	Hyperinsulinemia—hypoglycemia
Central nervous system:	Hyperbilirubinemia
Anencephaly, spina bifida	Hypocalcemia
Hydrocephalus	Polycythemia
Cardia:	Respiratory distress syndrome
Ventricular septal defect	Birth asphyxia
Gastrointestinal tract:	
Gastroschisis	
Small left colon syndrome	
Skeletal:	
Caudal regression syndrome	
Absent left femur	
Intrauterine growth retardation	
During third trimester	
Macrosomia	
Organomegaly	
hypertrophic cardiomyopathy	
Renal vein thrombosis	
Birth injuries secondary to macrosomia	
Erb's palsy	
Fractured clavicle	

The presence of a significant structural defect can be detected by ultrasound early in pregnancy, providing an opportunity for either intervention and treatment, or termination of pregnancy if deemed necessary. Other means of detecting major neural-tube defects includes measurement of maternal and/or amniotic fluid alpha-fetoprotein, an oncodevelopmental protein which is elevated in pregnancies complicated by open neural-tube defects, including meningomyelocele (11, 12).

Macrosomia and Hypoglycemia. It has been shown that macrosomia results from the accumulation of adipose tissue and from increased protein and glycogen in organs, and is not manifested until after 32 weeks' gestation (13). Similarly, hypoglycemia, thought to be the result of both increased insulin in the pancreas and greater insulin sensitivity due to increased insulin receptor numbers, is a phenomenon of the last trimester of pregnancy, at a time concordant with both insulin synthesis by the pancreas and maturation of the insulin receptor (14, 15).

The factors which contribute to these pathophysiologic events in the offspring of diabetic pregnancies are uncertain; however, there is evidence to support the Pedersen hypothesis that maternal hyperglycemia leads to increased levels of insulin in the fetus, which in turn lead to the abnormalities described (16). Indeed, Whitelaw (17) has shown that neonatal adiposity, as determined by subcutaneous skinfold thickness, correlated extremely well with maternal glucose levels measured during the third trimester.

The data suggest that maternal glucose serves as a substrate for fetal growth. This is supported indirectly from observations in pregnancies complicated by maternal hypertension and placental vascular insufficiency. Under these circumstances, it has been shown that provision of glucose to the fetus is reduced, and that this is associated with a reduction in birthweight resulting from intrauterine growth retardation (18).

Arguing against a causal role for maternal hyperglycemia in the pathogenesis of fetal macrosomia are several recent reports concerning the occurrence of macrosomic infants born to mothers whose diabetes was rigidly controlled by continuous subcutaneous insulin infusion via portable insulin pumps. In several cases, random blood glucose values in these patients were below normal, and glycosylated hemoglobin levels were also not different from normal (19–21). The presence of significant macrosomia and rapid growth rate can be detected by ultrasound performed during the last trimester of pregnancy (13).

Postnatal hypoglycemia is a frequent complication in offspring of poorly controlled or unrecognized diabetic pregnancies (22). This also has been attributed to the maternal-hyperglycemia–fetal-hyperinsulinism sequence; indeed, such infants do exhibit increased levels of insulin in cord blood and peripheral blood following birth (16). At autopsy, Driscoll and Steinke (23) also observed pancreatic islet hyperplasia with increased B cells in tissue from infants of diabetic mothers. Unlike the effect of high insulin concentrations in postnatal subjects, which results in down-regulation of the insulin receptor in a "self-protective" gesture associated with reduction in sensitivity to the hormone, no such process appears to be operative in the fetus (24, 25).

In offspring of gestational diabetic mothers who exhibited hyperinsulinemia at birth, there was a fourfold increase in insulin receptor binding to their cord blood monocytes when compared to those from gestational-age matched controls (Fig. 2). Furthermore, a direct correlation was observed between birthweights and the tracer binding of insulin to monocytes from control and gestational-diabetic pregnancy, further supporting a role for fetal hyperinsulinemia in the development of macrosomia (24, 25).

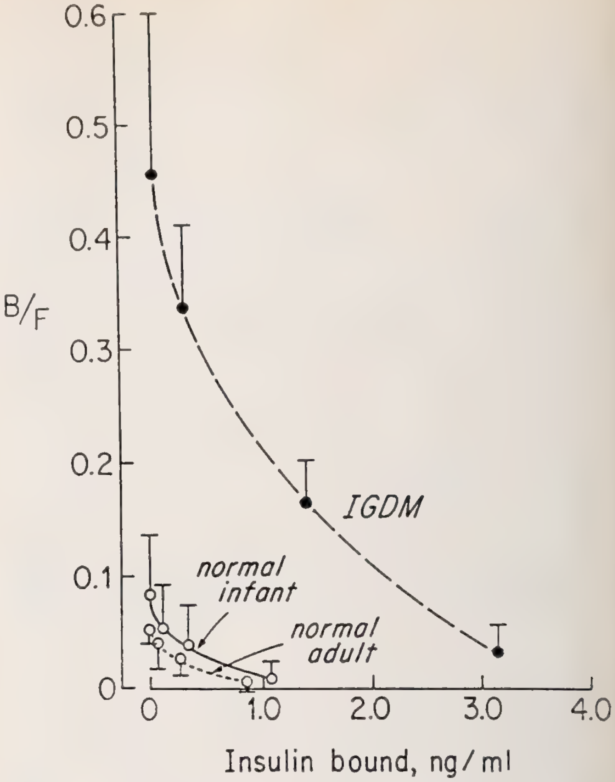

Fig. 2. Scatchard plot of ^{125}I-insulin binding to monocytes from normal adults, normal newborns, and infants of gestational diabetic mothers. All data were normalized to a concentration of 5 × 10^6 cells/ml (14). *Reprinted with permission from the Endocrine Society*

Frank Respiratory Distress Syndrome. The incidence of frank respiratory distress syndrome, resulting from deficiency of surfactant in the neonatal lung, is lower now in infants of diabetic mothers, due to the introduction of newer techniques for prenatal diagnosis as well as the ability to permit pregnancies to be carried to term (22, 26, 27). Nonetheless, some cases of respiratory difficulty, usually due to transient tachypnea of the newborn, have been identified in offspring of class A diabetics. Early studies on the use of the lecithin: spingomyelin (L:S) ratio in amniotic fluid for detection of lung maturity showed that offspring of mothers with diabetes, classes A–C, exhibited delayed maturation, whereas those with longstanding diabetes (classes D, F, and R) exhibited mature lungs (28).

Studies both in vivo and in vitro support the hypothesis that fetal lung surfactant synthesis, and particularly the major component of surfactant, disaturated phosphatidylcholine, is inhibited by hyperinsulinemia (29–31). Thus it appears reasonable that hyperinsulinemia itself may play a role in this process in the fetal lung. By reducing the level of fetal hyperinsulinemia in offspring of diabetic mothers through strict diabetic control, the incidence of respiratory distress has fallen significantly (27).

Hypertrophic Cardiomyopathy. A newly recognized finding in some offspring of diabetic mothers is the occurrence of hypertrophic cardiomyopathy, which is associated with congestive heart failure in the newborn period (32, 33). It is diagnosed by the presence of cardiomegaly on chest X-ray and confirmed by detection of septal hypertrophy on echocardiogram (34). The course of this disorder is one of gradual regression, usually demonstrated by resolution of symptoms within 2–4 weeks and complete resolution of hypertrophy within 12 months. This disorder was first recognized in offspring of mothers with poorly controlled diabetes, since it is more commonly seen in those subjects with severe neonatal hypoglycemia. At autopsy, intraventricular septi from affected infants have demonstrated myofibril disruption and glycogen accumulation (32, 34).

Hyperbilirubinemia and Gestational Diabetes. Hyperbilirubinemia appears to be the most common disorder observed in offspring of gestational diabetic mothers, accounting for nearly 25% of cases which demonstrate perinatal morbidity (22). The etiology of hyperbilirubinemia in these subjects is unclear; in most infants the predominant form of circulating bilirubin is the unconjugated form, suggesting impairment or lack of maturation of the glucuronidation system. This is supported by the findings of Stevenson et al. (35), who demonstrated delayed clearance of bilirubin in these infants assessed by measurements of pulmonary carbon monoxide excretion. It is also possible that polycythemia, which has been observed in as many as 40% of offspring of diabetic mothers, contributes to the markedly higher rates of bilirubin production (22). Increased erythropoeisis in offspring of diabetic pregnancies is probably due to increased levels of erythropoetin observed in these infants, the latter attributable to some degree of anoxia experienced by these infants prior to delivery (36). In addition, the occurrence of birth trauma and hematoma formation, resulting from macrosomia and associated with resultant hemoglobin breakdown, has been suggested as a possible contributing factor to this phenomenon (37).

Stillbirths. Perhaps the most tragic consequence of diabetic pregnancy is the risk of stillbirth, a poorly understood event which often occurs without warning in the last weeks of pregnancy (38). Although some authors have suggested that fetuses of such pregnancies might suffer from profound hypoglycemia, as evidenced by extremely low glucose-to-insulin ratios, an alternative explanation might rest in the relative resistance of these infants to the actions of catecholamines, perpetuating the hypoglycemic stress (39, 40). Very little is known about the cause of this fatal complication of diabetic pregnancy, a fact which is reflected in the lack of any significant reduction in its incidence or occurrence.

Incidence and Gestational Diabetes. From the previous discussion, it should come as very little surprise that offspring of mothers whose diabetes antedates the first trimester should have a greater incidence of structural anomalies than those who are identified late in pregnancy. Recently, Widness et al (41) have shown that women who were recognized as being mildly glucose intolerant during the last trimester of pregnancy had a significantly greater likelihood of giving birth to infants with congenital anomalies. The data from this and other studies suggest that some disorder in maternal metabolism must be present early in pregnancy. It is possible that unrecognized type 2 (insulin-dependent) diabetes is present in some of these patients prior to conception. In some studies, in fact, it has been shown that subjects classified as having gestational diabetes or mild carbohydrate intolerance during pregnancy did not revert to normal following delivery and indeed had type 2 diabetes mellitus, which was presumed to be present early in pregnancy (3). O'Sullivan observed that nearly 10% of patients with gestational diabetes fell into this category (2).

Recognition and Treatment of Disorders in Infants of Diabetic Mothers

If maternal blood glucose values are normalized during pregnancy [see articles under heading Treatment in this issue], the infant requires very little other than routine newborn care, since the incidence of perinatal morbidity has been shown to be reduced to normal rates when the mother's blood glucose is normal. On the other hand, if the mother does not achieve normal blood glucose during pregnancy, the infant requires more careful monitoring, with attention to the presence of both structural and functional disorders.

Incidence and Severity. The incidence and severity of the specific problems of the infant of the diabetic mother are related directly to the severity of maternal diabetes, as well as to the degree of prematurity at birth (43). Near-term infants born to mothers with gestational diabetes have a reported incidence of perinatal morbidity of 25% or less (22). On the other hand, infants delivered prior to 36 weeks' gestation to mothers whose disease was more severe and difficult to control early in pregnancy have morbidity rates which approach 60% or greater (26). In particular, these infants have been observed to have a greater incidence of serious complications, including major congenital malformations.

Data Needed. Following delivery, essential information—including Apgar score, weight, sex, and the presence of any major structural anomalies—should be recorded. A specimen of cord blood should be sent for determination of glucose and pH. Infants are transferred to the newborn nursery, where a more thorough examination can be performed. Assessment of gestational age by Dubowitz examination is recorded (44). Detailed examination of heart, lungs, kidneys, and extremities, as well as examination for structural anomalies and injuries including Erb's palsy, fractured clavicle, or phrenic nerve injury in macrosomic infants, should be performed. Blood studies for determination of serum glucose, calcium, hematocrit, and bilirubin are performed at frequent intervals during the first 48 hours after birth (43).

Hypoglycemia. Hypoglycemia is defined as a blood glucose value of 30 mg/dL or less in the full-term newborn (20 mg/dL in the preterm infant). Treatment for this disorder can be started prophylactically in the form of early feedings (glucose water given within the first hour following birth has been associated with a reduction in the frequency of symptomatic hypoglycemia). Assessment of blood glucose values in association with frequent feedings should continue until the infant is stable. In more severe cases, where hypoglycemia is intractable, the use of adjunct measures such as glucose infusion or Diazoxide may be necessary. In the majority of infants, however, breast or bottle feedings are tolerated within the first twelve hours, and these feedings combined with supplemental feedings of glucose water may be sufficient to prevent hypoglycemia (43).

Elevated Hematocrit. The occurrence of an elevated hematocrit (over 65%) is very common in infants of diabetic mothers, although the exact incidence is not known. The clinical findings in such infants are due to the increased viscosity of blood flow in the venous bed and include respiratory distress, cyanosis, jitteriness, jaundice, thrombocytopenia, necrotizing enterocolitis, and gangrene. Treatment is aimed at lowering the hematocrit to between 50%–60% by means of exchange transfusion (43).

Polycythemia and Renal Vein Thrombosis. Renal vein thrombosis is an unusual complication of polycythemia and is more frequent in infants of diabetic mothers. Clinical manifestations include hematuria and renal enlargement. Treatment is conservative and is based on careful management of fluid and electrolytes, coupled with heparin treatment. These are temporizing measures that permit observation for spontaneous resolution of the disorder. In rare instances, surgical intervention may be required.

Treatment for the more severe disorders seen in diabetic pregnancy, including respiratory distress syndrome and major structural anomalies, is discussed in standard neonatology textbooks and is beyond the scope of this review. As stated previously, with careful supervision of maternal diabetes during pregnancy, these disorders are observed with decreasing frequency. The goal of programs such as the one in our institution is to assure the diabetic woman of a normal healthy infant at birth.

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The Mount Sinai Journal of Medicine Awards 1986/87

Ralph Colp Prize

Leon Morgenstern

The 1986/87 Ralph Colp Prize for the best surgical paper published in *The Mount Sinai Journal* during the academic year went to Leon Morgenstern, MD, FACS, for his article "Near-Total Splenectomy for Massive Splenomegaly due to Gaucher Disease" (vol. 53, no. 7). His co-authors were Edward H. Phillips, MD, FACS, David Fermelia, MD, and Irwin M. Weinstein, MD, FACP. Dr. Morgenstern is Director of Surgery at Cedars-Sinai Medical Center, Los Angeles. This and the other *Journal* prizes were presented at the Mount Sinai School of Medicine graduate awards ceremony May 29, 1987.

Globus Prize

The 1986/87 Globus Prize for the best clinical paper published annually in *The Mount Sinai Journal* went to Sumumu Ono, MD, for his paper "The Function of the Autonomic Nervous System and Nonautonomic Components in Juvenile Patients with Hypertension" (vol. 53, no. 2). Dr. Ono is with the Second Department of Internal Medicine, School of Medicine of Kanazawa University, Kanazawa, Japan. The award honors Joseph H. Globus, founder and first editor of the *Journal.*

Student Prize

Jeffrey I. Mechanick

The 1986/87 Student Prize for the best student paper published annually in *The Mount Sinai Journal* has been awarded to Jeffrey I. Mechanick, MD, for "Methods of Creative Cognition in Medical Diagnosis" (vol. 54, no. 4), written when the author was a third-year student at Mount Sinai School of Medicine (CUNY). Dr. Mechanick is currently a resident in internal medicine at Baylor College in Houston. He hopes to return to New York for a fellowship in endocrinology at Mount Sinai.

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Cardiovascular Effects of Opioid Anesthesia

CARL E. ROSOW, M.D., PH.D.

When modern "balanced" anesthesia was introduced in 1947, the intraoperative uses of opioids were perceived in a rather specific fashion: low doses of morphine or meperidine were used to produce analgesia, whereas amnesia or sleep was produced by potent hypnotics like the barbiturates. Opioids served to blunt autonomic responses to surgical stimuli and to reduce the requirement for other anesthetic agents. In this setting, the cardiovascular effects of the morphinelike drugs are minuscule when compared with the hemodynamic responses to surgery itself. Until recently, most textbooks of medical pharmacology mentioned only that morphine could produce bradycardia and mild vasodilation —useful effects if a patient were in pulmonary edema, not so useful if he or she tried to walk.

The advent of so-called "high-dose" opioid anesthesia changed our perspective somewhat. Opioid effects once thought trivial (like sedation and vasodilation) suddenly became important. In 1969 Lowenstein et al showed that 1 mg/kg of morphine could be given safely to patients with limited myocardial reserve undergoing aortic valve surgery (1). The opiate produced a state of sedation or hypnosis with profound analgesia—that is, anesthesia—while allowing these compromised patients to maintain an acceptable cardiac output. Ironically, as cardiovascular surgical procedures increased in number, this technique was widely applied (or misapplied) to relatively fit patients undergoing coronary artery bypass grafting. It is in this latter group of patients that the limitations of opioid anesthesia are most evident.

It is probably not an overstatement to say that most cardiovascular surgery in this country is performed under some variant of high-dose opioid anesthesia. Morphine has been largely supplanted for this use by fentanyl and the new fentanyl congener sufentanil. In this paper I review briefly the cardiovascular effects of these three opioids. More important, I consider the use of the opioids as "anesthetics" and the ways in which these drugs may modify the hemodynamic responses to surgery.

Effects on Contractility

In their classic 1933 paper, Schmidt and Livingston described many of the important hemodynamic effects of morphine (2). They noted that hypotension and bradycardia occurred in most species at doses that did not have negative inotropic effects. In isolated muscle preparations (e.g., cat papillary muscle) many opioids have been shown to decrease contractility, but only at concentrations in excess of 10^{-4} M (approximately 30 μg/ml morphine) (3). In isolated saline-perfused rabbit hearts morphine concentrations of 100 μg/ml were required to depress dP/dt_{max} (4). In comparison, intravenous administration of 2 mg/kg of morphine in humans may briefly produce a plasma concentration of 1–2 μg/ml (5). This separation of therapeutic and cardiac depressant concentrations is even greater for the potent synthetic opioids.

Experiments with morphine in intact an-

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imals or humans frequently show positive inotropic responses. Although morphine does not directly release adrenal catecholamines, it may frequently elicit sympathetic reflex responses (6). These responses may also be due to histamine release and the direct effects of this amine on adrenal and/or myocardium (vide infra).

Effects on Heart Rate

Morphine and fentanyl (and presumably sufentanil) produce bradycardia by stimulation of central vagal preganglionic neurons (7, 8). This effect is mediated by typical stereospecific opiate receptor mechanisms in the medulla, and it may be blocked or reversed with naloxone, vagotomy, or vagolytic drugs. Meperidine, an opioid with weak atropinic effects, may produce tachycardia in higher doses (9).

Effects on Peripheral Vasomotor Tone

A decrease in peripheral vascular resistance occurs with even low doses of most opioids. Studies in both animals and humans indicate that morphine dilates both resistance and capacitance beds, but it does so by different mechanisms. The proposed mechanisms for arteriolar dilation include (a) direct (local) effects on vascular smooth muscle, (b) inhibition of medullary sympathetic outflow, and (c) histamine release.

Direct Effects. The existence of a direct vasodilator effect of the opioids is controversial. Direct intraarterial injection of morphine into denervated, separately perfused canine gracilis muscle was reported to decrease gracilis vascular resistance (10). I have recently found that the morphine concentrations used in this study were high enough to produce substantial local histamine release (Rosow, unpublished observations). Sufentanil failed to produce direct vasodilation in the same experimental preparation (Rosow, unpublished observations).

Samuel et al suggested that intravenous morphine can produce vasodilation in the human forearm even after brachial plexus blockade (that is, peripheral sympathectomy) (11). However, injection of morphine into the human brachial artery does not appear to produce direct vasodilation (12). The reasons for these discrepancies are not obvious.

Altura et al have reported that close intraarterial injection of morphine, meperidine, levorphanol, or codeine causes dose-related dilation of terminal arterioles in rat mesentery (13). These authors have suggested that the effect is mediated by opiate receptors in the vasculature, although direct proof of this is lacking.

Neurally Mediated Effects. Lowenstein et al studied the effects of intravenous morphine in an innervated, separately perfused canine gracilis preparation (10). Dogs were either hemorrhaged or transfused to raise or lower baseline gracilis vascular resistance, and then morphine was given intravenously. Only the hemorrhaged animals (i.e., those with initially elevated peripheral resistance) responded to morphine with a drop in gracilis vascular resistance. Since morphine does not reach the gracilis artery in this preparation, the effect must be neurally mediated. The clinical implications of this study are worth emphasizing: patients who are critically ill and those with underlying cardiac disease usually have high levels of sympathetic tone, and it is this group which has the greatest hemodynamic response to the opioids. In Lowenstein's original study of morphine anesthesia, "normal" patients did not have a predictable change in total peripheral resistance after morphine, whereas cardiac patients had a consistent decrease (1). Similar findings have been described when cardiac patients were given fentanyl (14).

Studies by Zelis et al and Laubie et al show that morphine and fentanyl produce a "central sympatholysis," that is, a reduction in alpha-adrenergic tone mediated by an action on opiate receptors in the central nervous system (15, 16). In contrast, these opioids do not alter the arteriolar response peripherally. Ward et al showed that morphine did not affect the increase in canine hindlimb vascular resistance produced by norepinephrine infusion or by stimulation of sympathetic nerves (17). The clinical lesson is important here as well: opioids are not alpha- or beta-blockers. They decrease reflex sympathetic activation by modulating neurotransmission in afferent pain pathways. Sympathetic activation and catecholamine release may also be due to a variety of stimuli having nothing to do with pain, and opioids will not block these. Whatever the cause, once hypertension and tachycardia have been elicited, they are unlikely to be treated effectively by the administration of an opioid.

The mechanism for venodilation seems to be different from that in arteries, since sympathetic control is affected peripherally. In the study by Ward described above, morphine produced dose-dependent antagonism of the venoconstrictor responses to peripheral sympathetic nerve stimulation or norepinephrine infusion (17). The time course of the arterial and venous responses is different as well. In halothane-anesthetized patients on cardiopulmonary bypass, systemic morphine produces a rapid, short-lived drop in resistance, whereas the capacitance changes occur more slowly and last longer (18). Capacitance "paralysis" may explain the observation that extremely high doses of morphine produce splanchnic pooling and greatly increase perioperative fluid and blood requirements during cardiac surgery (19). It is unclear to what extent this occurs during fentanyl or sufentanil anesthesia.

Histamine-Mediated Effects. Histamine is released from tissue mast cells by a variety of low-molecular-weight basic amines, among them opioid alkaloids. Morphine, meperidine, and codeine produce the cutaneous signs of histamine release (redness, itch, urticaria), but usual analgesic doses do not elevate plasma histamine in most individuals. Elevation of plasma histamine has now been demonstrated in humans following large doses of morphine and meperidine, and there is a moderately strong negative correlation between plasma histamine and total peripheral resistance (20, 21). Pretreatment of patients with a combination of diphenhydramine and cimetidine markedly reduces the early drop in systemic pressure and resistance after morphine, although plasma histamine still rises (22). Even very large doses of fentanyl and sufentanil produce no measurable increases in plasma histamine (20, 23).

Opioids as Anesthetics

A rather pointless debate continues in the anesthetic literature over the merits of "pure" opioid versus inhalation anesthesia for the cardiac surgical patient. The purported advantage of morphine-oxygen anesthesia was "hemodynamic stability," and there is little doubt that high-dose morphine had advantages over other anesthetic agents available during the late 1960s: there was little reduction in cardiac output, peripheral vasodilation was usually mild and easily treated, there was no sensitization to catecholamines, and arrhythmias were not common. Unfortunately, even these doses of morphine did not eliminate all hemodynamic responses to surgery, and a large number of patients had recall for some part of their surgery.

Stanley attempted to produce a more satisfactory anesthetic by giving doses of 9–10 mg/kg of morphine (19). This produced unacceptable levels of hypotension, probably secondary to splanchnic pooling and histamine release, with resulting fluid loss to tissues.

Fentanyl. Fentanyl unquestionably has advantages over morphine in this setting, since the recommended doses of 50–150 μg/kg (equivalent to >10 mg/kg of morphine) produce only modest decreases in systemic pressure and peripheral resistance. In spite of the intense narcotic effect, intraoperative hypertension, especially during sternotomy and manipulation of the great vessels, is a common occurrence during fentanyl anesthesia (24). Awareness is not as common a problem, but cases of recall have been reported with doses as high as 90 μg/kg (25).

For several years we have debated ways to improve fentanyl-oxygen anesthesia. Intraoperative hypertension has been variably attributed to insufficient fentanyl (unlikely), insufficient beta-blockade (possibly), or patient drug history (nothing we can change). Most clinicians simply add a vasodilator or inhalation anesthetic to control the immediate pressure problem. The usual approach to prevent awareness is the addition of supplemental hypnotic agents such as diazepam. Unfortunately, diazepam can produce marked vasodilation and hypotension when combined with high-dose fentanyl (26). This effect probably occurs by a further decrease in central sympathetic tone (27). It is also a reminder that, in contrast to the volatile anesthetics, the opioids are *selective* central nervous system depressants. Any supplemental drug that "completes the anesthetic" may produce hypotension in this manner.

Sufentanil. The latest chapter in this story has unfolded with the introduction of sufentanil. Sufentanil seems to share fentanyl's hemodynamic advantages as an opioid anesthetic and is tolerated in huge doses (up to 30 μg/kg, the analgesic equivalent of 20–30 mg/kg of morphine). It was hoped that this potent opioid would produce an anesthetic state with even less fluctuation in heart rate and blood pressure than fentanyl, and several clinical trials have suggested as much (28, 29). We compared fentanyl with sufentanil in a double-blind study of patients undergoing coronary bypass grafting (30). Although both agents produced good anesthetic conditions, intraoperative hypertension requiring treatment occurred in most patients: 6 of 10 patients receiving the highest dose of sufentanil (30 μg/kg) became hypertensive at sternotomy or aortic cannulation. There were no significant differences between fentanyl and sufentanil in requirement for vasodilators or volatile anesthetics. If the intrinsic activities of the two opioids differed, we were unable to demonstrate it in this study.

Usefulness. What can we conclude about fentanyl and sufentanil as anesthetic agents? These potent opioids are excellent induction agents, especially in severely compromised patients. On the other hand, additional anesthetics are sometimes needed for maintenance, especially in fit patients. Wynands et al have shown elegantly that intraoperative hypertension is much more an indicator of adequate myocardium than inadequate fentanyl (31). It is precisely the patient with good ventricular function who needs (and should receive) supplemental anesthetic drugs.

The goal of "stress-free" opioid anesthesia has been a will-o'-the-wisp at best, and I disagree with the notion that any opioid can or should be used to suppress all responses to everything. Indeed, preservation of cardiovascular reflex activity may be one reason that opioids are so well tolerated by critically ill patients.

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Anesthetic Interactions with Beta-Blockers and Calcium Channel Blockers

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Beta-Blockers and General Anesthetics

In recent years, the medical management of patients with coronary artery disease and hypertension has been significantly improved because of agents such as beta-blockers. Owing to the development of new cardioselective and long-acting beta-blockers, coupled with the recommendation, based on several excellent studies, that beta-blocker therapy not be withdrawn prior to surgery, more patients who have received beta-blocker therapy on the day before or the day of surgery are coming to the operating room for anesthesia and surgery (1–5). Because both general anesthetics and beta-blockers have profound effects on the cardiovascular system, it is important for the anesthesiologist to be aware of any effects the combination of these drugs might have. Beta-blockers act by blocking endogenous and/or exogenous catecholamines at the beta-receptor; hence it is logical that those anesthetic agents most dependent on catecholamines for maintenance of hemodynamic stability would be most affected by the administration of beta-blockers.

In a study published in 1966 by Craythorne and Huffington examining the hemodynamic effects of ether and cyclopropane on dogs, it was shown that when propranolol was administered, the dogs sustained a decrease in cardiac output, heart rate, and blood pressure (6). Both ether and cyclopropane are anesthetics which are greatly dependent on circulating catecholamines for maintenance of blood pressure; therefore, propranolol blockade of circulating-catecholamine receptors results in hemodynamic instability. A number of controlled studies have shown an additive depression of the circulation when anesthetics and beta-blockers are combined (7, 8). But, as is common in anesthesia, there is a spectrum of effect; anesthetics such as methoxyflurane and cyclopropane are the most affected by simultaneous administration of beta-blockers, whereas narcotics and isoflurane, on the other end of the spectrum, are the safest to use in combination with beta-blockers.

Inhalation Agents. In 1975, Saner et al reported the results of a study in which they examined dogs anesthetized with various inhalation anesthetics and administered beta-blocking agents acutely (9). They observed that when dogs were anesthetized with 0.4% methoxyflurane in combination with intravenous practolol, 3 of 10 dogs died within 15 min. They demonstrated a decrease in contractility with an increase in left ventricular end-diastolic pressure, systemic vascular resistance, and maintenance of heart rate and mean arterial pressure. These findings were in contrast to results of hemodynamic stability with practolol and propranolol during halothane anesthesia, as reported by the same group in earlier studies (47).

A case report by Viljoen et al, published in 1972, claimed irreversible circulatory depression

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after cardiopulmonary bypass in a patient who had taken methoxyflurane and propranolol (10). This report was one of the earliest clinical warnings alerting anesthesiologists to the potential danger of combining beta-blockers with anesthetic agents.

In 1976, Philbin and Lowenstein examined the effects of beta-blockers in combination with isoflurane (11). Dogs were divided into three groups: a control group receiving isoflurane, 2 MAC; a second group receiving isoflurane in combination with propranolol, 0.1 mg/kg intravenously; and a third group receiving isoflurane, 2 MAC, plus propranolol, 0.5 mg/kg intravenously. The authors found no difference between study groups in hemodynamics measured: cardiac output, blood pressure, systemic vascular resistance, heart rate, and pulmonary capillary wedge pressure. The authors concluded that isoflurane may be safely administered in combination with propranolol and that isoflurane had little, if any, beta-adrenergic, agonist effect.

In studies by Horan et al published in 1977, the observed effect of combining beta-blockers with enflurane and isoflurane was an additive depressive effect between enflurane and beta-blockers and isoflurane and beta-blockers (12, 13). Enflurane was more depressive than isoflurane when combined with a beta-blocker in this protocol.

By varying the depth of anesthesia, Horan et al found a differential "light" and "deep" effect of beta-blockade on the hemodynamics of dogs anesthetized with isoflurane. This evidence indicated a possible beta-agonist effect of isoflurane, in opposition to Philbin and Lowenstein's conclusion (11). Rather than a beta-agonist explanation for these findings, the data are consistent with the fact that at "light" levels of anesthesia, there are increased levels of circulating catecholamines which would be responsible for the differential effect.

In studying the effects of beta-blocker administered with halothane, Merin and Tonnesen found that the arrhythmogenic dose of epinephrine required was greater in dogs administered beta-blockers than in those not administered beta-blockers (14).

Furthermore, a study by Foex and Ryder showed that for circulatory effects, varying the beta-blocker administered is as important as varying the administered anesthetic agent (15). For example, it is believed that pindolol, oxprenolol, and practolol are all beta-blockers which possess intrinsic sympathomimetic activity (16). This means that these agents contain some beta-agonist activity and therefore cause less depression to the cardiovascular system when administered either alone or in combination with general anesthetics.

When considering the effects of general anesthetics on the circulation, it is important to know what the status of ventilation is. For example, in dogs anesthetized with 1% halothane and with hypercarbia induced by hypoventilation, an increase in heart rate, cardiac output, and contractility occurs, along with a decrease in systemic vascular resistance (17, 48). When propranolol was administered to these dogs during hypercarbia, all of the above changes were blunted (17). In contrast, when hypocarbia caused increased heart rate, decreased cardiac output and contractility, and increased systemic vascular resistance, propanolol also blunted these changes.

Foex and Prys-Roberts repeated this study, substituting nitrous oxide for halothane, and found an exaggerated increase, as compared to halothane, in heart rate, cardiac output, and contractility to induced hypercarbia and an exaggerated increase in heart rate, decrease in cardiac output, and decrease in contractility to hypocarbia (17). All of these responses were blunted with propranolol (17).

When propranolol is administered with inhalation anesthetics, the additive myocardial depression varies from agent to agent. Of the major inhalation agents, enflurane has the strongest depressive effect, followed by halothane and isoflurane in order.

Despite these depressive effects, studies in both humans and animals all yield the conclusion that beta-blockers are safe to use in patients anesthetized with inhalation agents (12, 13, 19). Furthermore, a more pronounced beta-blockade-induced depression of the circulation is seen in patients with "light" levels of anesthesia, probably as a result of an increased level of circulating catecholamines.

Narcotics. When beta-blockers are administered to patients anesthetized with narcotics, there are certain observable hemodynamic affects. In a study by Berthelsen et al, dogs were administered propranolol, 2.0 mg/kg intravenously, and total beta blockade was confirmed with an isoproterenol challenge. These dogs were then divided into two groups; the first received morphine sulfate, 4.0 mg/kg, and the other received sufentanil, 0.01 mg/kg (20). Both groups demonstrated decreases in cardiac output of approximately 40%, but the morphine group demonstrated a decrease in mean arterial pressure of approximately 65%, whereas the sufentanil group maintained mean arterial pressure. The decrease in cardiac output in the sufentanil group was most likely a result of a decrease in heart rate and an increase in systemic vascular resistance. Oxygen consumption fell by 20% in the sufentanil group and was unchanged in the morphine group. In the same protocol, the authors measured mixed venous pH and muscle surface pH and found that both these parameters were stable in the sufentanil group, but noted that acidosis developed in the morphine group (21)—pH fell to 7.14 from a baseline of 7.34.

Thiopentone, in combination with propranolol, prolonged sleep time, as demonstrated by Mason and Angel (18, 22). This increase in sleep time was reversed by a central beta-agonist, and therefore, the mechanism proposed was a central beta-blockade effect with thiopentone. In addition, no central nervous system effect was noted in animals treated with metoprolol and atenolol, both of which are selective beta-1-blockers (22). Study to date has demonstrated no effect on MAC by the administration of beta-blockers to either humans or animals.

Calcium Channel Blockers and Anesthetics

Calcium channel blockers may exert a variety of hemodynamic effects, including alterations of heart rate, contractility, and systemic vascular resistance. The specifically observed effect is dependent on which calcium channel blocker is administered, the dose, and the route of administration, as well as the status of compensatory reflexes. Furthermore, the particular hemodynamic effect depends on what other drugs, if any, are being concurrently administered.

In a study by Kapur et al, intravenous verapamil was infused in three groups of dogs, anesthetized with either isoflurane, enflurane, or halothane (23). Verapamil was infused to various plasma levels, and each level was maintained through various hemodynamic measurements. It was demonstrated that enflurane exhibited the greatest decreases in left ventricular DP/DT, mean arterial pressure, and cardiac index. Isoflurane showed decreases in all these parameters as well, but only at much higher plasma levels of verapamil. The only hemodynamic effect demonstrated in the halothane group was prolongation of the PR interval. None of the hemodynamic effects seen in the isoflurane group were demonstrated at plasma levels in the therapeutic range for arrhythmia control in humans. Furthermore, the earliest decreases in mean arterial pressure seen in the isoflurane group were at what is considered to be a highly toxic dose of verapamil: in the range of 400–500 ng/ml.

In a fascinating study by Kates et al, eight dogs were placed in a right-heart bypass preparation and had their sinoatrial nodes crushed and heart rates maintained by atrioventricular pacing (24). These dogs were anesthetized with isoflurane and demonstrated concentration-related depression of ventricular DP/DT, left ventricular function curves, percent diastolic shortening, and systemic vascular resistance. Subsequently, with administration of verapamil, a dose-concentration enhancement of all four effects was demonstrated. Administration of calcium chloride partially antagonized all the effects seen with verapamil administration.

Patients scheduled for elective coronary artery bypass grafting, with normal left ventricular function and on long-term beta-blocker therapy, demonstrated a small, although additive, depression of contractility and a reflex decrease in systemic vascular resistance when anesthetized with halothane and administered either verapamil or nifedipine (25).

Halothane. Halothane-associated ventricular arrhythmias are believed to occur as a result of the failure of halothane to slow intraventricular conduction in the face of increased blood levels of catecholamines, with resultant arrhythmias of the reentrant type. In a study by Kapur and Flacke, the mean arrhythmogenic epinephrine dose during 1.1 MAC halothane was measured before and after administration of verapamil. A prompt and cumulative increase in the necessary epinephrine dose was demonstrated after verapamil infusion for initiation of ventricular arrhythmias (26). These results were not surprising in light of the fact that verapamil is used in the treatment of reentrant arrhythmias.

In a later study by the same authors, a dose-related depression of left ventricular function was demonstrated with the combination of verapamil and halothane (27). No change in heart rate was observed, although the PR interval increased significantly. Also noted in the same patients was a greater tolerance to isoflurane than enflurane when administered in combination with verapamil. In a study by Marshall et al, isolated rat hearts studied with isobolographic analysis showed that halothane, in combination with nifedipine, caused an additive negative inotropic effect (28).

In a recent study by Kates et al, three groups of swine anesthetized with halothane, 1.0 MAC, were given equihypotensive doses of verapamil, diltiazem, and nifedipine (30). End-tidal carbon dioxide was maintained constant, and all calcium channel blockers were given by intravenous infusion. As a control, a fourth group of swine was administered nitroprusside, in lieu of a calcium channel blocker.

This study demonstrated that the hypotension induced with these calcium channel blockers was of different mechanisms. Verapamil and diltiazem caused hypotension by decreasing cardiac output, whereas nifedipine and nitroprusside caused hypotension by decreasing systemic vascular resistance. Despite the differing mechanisms of decreased arterial pressure, calcium antagonized the hypotension in all groups by increasing cardiac output and stroke volume and decreasing systemic vascular resistance. As Reves pointed out in an editorial on this study, important information is gained from this work (31). At equihypotensive doses of the various calcium channel blockers, there is a relative potency scale of the effects of calcium channel blockers on various hemodynamic parameters demonstrated during 1.0 MAC halothane. But there are problems with this study: (a) it does not answer the question of chronic administration of calcium channel blockers, (b) no awake control values were measured to determine the effects of halothane, and (c) at present no intravenous preparations of diltiazem or nifedipine are available for clinical use.

Morphine-Valium-Nitrous Oxide. Patients anesthetized with morphine-valium-nitrous oxide anesthesia were administered a bolus dose of 0.075 ml/kg verapamil. All patients were scheduled for coronary artery bypass grafting and had good preoperative left ventricular function. The authors observed decreases in systemic vascular resistance and mean arterial pressure of approximately 30%, with no change in pulmonary capillary wedge pressure or cardiac index (32).

In a study by Zimpfer et al, healthy patients with no history of cardiac disease who were to undergo abdominal surgery were anesthetized with narcotic anesthesia and administered a bolus dose of 0.07 ml/kg verapamil (33). A decrease in systemic vascular resistance and mean arterial pressure was demonstrated, with no change in heart rate or pulmonary capillary wedge pressure. A transient increase in cardiac output was demonstrated. These results were similar to those found by the previous authors. The mechanism of the hypotension seen with calcium channel blockers, administered in combination with narcotics, was postulated to be a result of the greater baseline plasma-catecholamine levels seen after long-term calcium channel blocker administration (34, 35). These increased plasma levels of catecholamines result in greater decrease in blood pressure when these patients are anesthetized with high-dose narcotic anesthesia (36, 37).

Mage and Mason demonstrated a decrease in halothane MAC from 0.97% to 0.72% in dogs administered 0.5 mg/kg verapamil. A proposed mechanism of this decrease in MAC was a local-anesthetic-like sodium channel blockade (29).

Neuromuscular Blockers. When examining the effects of channel blockers used in combination with neuromuscular blockers, it must be kept in mind that no controlled human studies have been performed to date. Animal studies have shown interspecies variation, but are suggestive of an important action of the calcium channel blockers at the neuromuscular junction. It has been demonstrated that the effects of depolarizing neuromuscular blockers are augmented by administration of verapamil (39, 40). Furthermore, verapamil and nifedipine have been shown to cause a reduction in twitch height in a dose-related fashion (38). Diltiazem has also been shown to augment indirect twitch tension when administered to dogs (41–43). No difference in reversal of neuromuscular effects has been demonstrated when a combination of calcium channel blockers and neuromuscular blockers is administered (38, 44).

Two case reports in the literature implicate the neuromuscular affects of calcium channel blockers in humans. The first case report, published by Zalman et al in 1983, presents a patient with Duchenne's muscular dystrophy who developed atrial flutter. This patient was administered 6.0 mg of intravenous verapamil and developed precipitous apnea (45). The authors implicated neuromuscular blocker properties of verapamil in this event.

The second case report, by VanPoorten et al, is of a 66-year-old woman with dialysis-controlled renal failure (46) who developed intraabdominal sepsis and resultant supraventricular tachycardia, requiring administration of verapamil, 5.0 mg t.i.d. The patient was dialyzed the day prior to surgery, and all antibiotics were withheld for 3 days prior to surgery. After induction of anesthesia with thiopental, nitrous oxide, and oxygen, 8.0 mg of vecuronium was administered to facilitate endotracheal intubation. Ten minutes later, 2.0 mg of vecuronium was administered, and no further muscle relaxant was given until 90 min later, when 1.0 mg of vecuronium was given. The operation was completed 50 min after the last dose, and at that time the twitch was noted to be 20% of control. Over the next 90 min, 3.0 mg of intravenous neostigmine was administered to this patient to reverse the vecuronium. The authors judged this experience with vecuronium, in a patient with renal failure, to be unusual and implied that the prolonged dose-interval and prolonged recovery indicated that the verapamil was responsible for potentiating the neuromuscular effects of vecuronium. No other possibilities for this interaction or phenomenon were postulated by the authors.

Summary

In conclusion, as increased numbers of patients present for anesthesia and surgery on chronic and/or acute beta-blocker and calcium channel blocker therapy, clinicians must be aware of potential drug interactions between these agents and general anesthetics. The hemodynamic depression of the circulation seen with anesthetics is potentiated additively by these medications, but any specific effect will depend on which drugs are administered, dosages, route of administration, and the patient's status, as well as on compensatory reflexes.

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Is Isoflurane Best for the Cerebral Circulation?

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Historical Notes. For almost 100 years controversy has existed over which anesthetic technique best preserves cerebral function. Sir Victor Horsley, the father of British neurosurgery, experimented extensively on the function of the brain and spinal cord (1). Between 1883 and 1885 he studied the intracranial effects during surgery of ether, chloroform, and morphine sulfate. He concluded that ether increased arterial pressure and blood viscosity and promoted excessive bleeding, vomiting, and excitement after surgery and was therefore unsuitable for use in neurosurgery. He felt that morphine was of value because of the apparent decrease in cerebral blood flow and the greater ease with which hemorrhage could be controlled in the surgical field. He suggested a "balanced" technique using a combination of chloroform and morphine and in 1887 used this method for the first time to remove spinal cord tumors and perform craniotomies. He later abandoned morphine because of its respiratory depressant effects.

Fedor Krause, the acclaimed founder of German neurosurgery, preferred to use chloroform alone (1). In the United States, Harvey Cushing's preference was for cocaine infiltration. In 1929, a patient from whom he had removed a large intracranial cyst reported "one of the secrets of Dr. Cushing's success is that he uses nothing except a local anesthetic which permits the normal functioning of the heart and the organs during the operation" (2). His preference was also shared by DeMartel, who in 1913 adopted local infiltration for all types of neurosurgery.

Tribromethanol was used rectally and described by Walter Dandy in 1931 as a method of reducing intracranial pressure. Leo Davidoff, finding that the effects of tribromethanol wore off too quickly, described its use in combination with local infiltration. For many years, ether was the most popular agent because a normal, spontaneous respiratory pattern could be maintained, allowing the surgeon to assess the safety and wisdom of dissection around brain stem structures.

Recent Developments. As the use of electrocautery became integral to neurosurgery, nonexplosive, halogenated agents, such as halothane and methoxyflurane, were developed. The latter agent was described as a "nonexplosive ether" which allowed spontaneous respiration (3), but, because of high fat/blood solubility which delayed return to consciousness, nephrotoxicity, and a 50% in vivo metabolic breakdown, acceptance was limited (3).

Halothane, on the other hand, although much shorter-acting, increased cerebral blood flow and intracranial pressure, especially if brain compliance was reduced (4, 5). Studies a few years later suggested that enflurane had less effect on intracranial dynamics, especially if initial intracranial pressure was less than 20 mm Hg (6). Moreover, enflurane was much less arrhythmogenic than halothane when epinephrine was injected (7). But early observations with enflurane showed that involuntary motor activity or tonic clonic seizures or both could occur (8, 9). Closer examination of the electroencephalo-

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graphic pattern indicated that increasing depth of anesthesia was characterized by high-voltage spikes and the subsequent development of spike waves and burst suppression. Hypocarbia increased the incidence of cerebral irritability (10). Case reports suggested delayed postoperative generalized seizures might be attributed to enflurane (11).

More recently isoflurane, an isomer of enflurane, has been developed. This agent appears to have several favorable characteristics and fewer complicating effects than other halogenated agents on intracranial dynamics.

Many agents have been used intravenously to produce anesthesia. Few have survived the test of time. Thiopental was synthesized by Von Wiler and Tabern in 1930 and introduced into clinical practice by Lundy and Waters in 1934. A report by Shannon and Gardner in 1946 described its use for all types of neurosurgery (12), but its acceptance in this arena was short-lived after the introduction of halothane. Recently, indications of a cerebral protective effect of barbiturates have prompted renewed interest in this group of drugs.

Although opiates have been used for thousands of years to relieve pain, it was not until 1916 that the first intravenous use of a morphine-scopolamine mixture for general anesthesia was described by Elisabeth Bredenfeld. Morphine alone was considered unsafe because the surgical and toxic doses were too close. Approximately 70% of patients had to be restrained, yet several deaths were recorded. The first entirely synthetic opioid, meperidine, was introduced in 1933 by Eisleb and Schaumann. Although the drug was less potent, without some means of assisted ventilation it entailed respiratory depression, a major disadvantage. The first opioid antagonist, nalorphine hydrochloride, was introduced to clinical practice in 1951 by Eckenhoff, Elder, and King. Now some of the devastating side effects of respiratory depression could be reversed.

The latest generation of short-acting synthetic opioids—fentanyl, 100 times as potent as morphine; sufentanil, 10 times more potent than fentanyl; and alfentanil—has added a completely new dimension to intravenous anesthesia. These agents have a large safety margin and cause little cardiac depression or other organ toxicity. Because of the adoption of routine intubation and controlled ventilation, the continued use of intravenous opioids is assured.

Thus, after 100 years or more of experimentation, it is easy to mark the agents and techniques unsuitable for neuroanesthesia. To determine the best choice requires evaluation of a drug's effect under different circumstances.

Cerebral Blood Flow and Metabolism

Barbiturates depress the cerebral metabolism of functioning neurons in a dose-dependent fashion (13). At constant Pa_{CO_2}, decreasing cerebral blood flow (CBF) parallels reduction in cerebral metabolic rate of oxygen consumption (CMR_{O_2}). The mechanism is probably due to a decrease in neuronal function which reduces O_2 demand and appropriately decreases CBF (that is, coupling between CBF and CMR_{O_2} is maintained). At surgical levels of anesthesia, CMR_{O_2} in humans decreases by 36–45%.

The effects of narcotics on CMR_{O_2} and CBF, especially clinically, are less well defined (14, 15). Generally, at constant Pa_{CO_2} and temperature, premedicant doses have little effect on CBF or CMR_{O_2}. Intravenous fentanyl has been shown to produce dose-related decreases in CBF and CMR_{O_2} in rats. Maximal depression occurred at 100 μg/kg, at which CMR_{O_2} and CBF were decreased by 35% and 50%, respectively (14). Smaller doses of fentanyl (5 μg/kg or less) may have no effect on CMR_{O_2} (14). In dogs anesthetized with pentobarbital (30 μg/kg), fentanyl, 25 μg/kg, did not significantly change CBF or CMR_{O_2} or alter the cerebrovascular responses to hypoxia or hypercapnia or change the limits of autoregulation (16). In an hypoxic rat model, fentanyl given prior to an hypoxic insult did not preserve cortical adenosinetriphosphate or phosphocreatine or prevent the development of lactic acidosis. Morever, fentanyl had no effect on cerebral energy metabolites (17). High-dose sufentanil has also been shown to reduce CBF and CMR_{O_2}, with maximum decrease of 53% and 40%, respectively, occurring at a dose of 80 μg/kg. Higher doses caused no further significant changes (18).

In normotensive, normocapnic volunteers, 1 MAC halothane increased CBF, an effect not seen at similar concentrations of isoflurane (19). However, at 1.6 MAC, cerebral blood flow doubled with both isoflurane and enflurane and nearly quadrupled with halothane, an increase that may be increased further by nitrous oxide (20, 21). A lower critical regional CBF with isoflurane than with halothane suggests a greater decrease in CMR_{O_2} with the former agent and an apparent cerebral protective effect (22). Other studies in rats have shown that, under conditions of normocapnia, isoflurane does not affect regional CBF at 0.5 MAC and 1.0 MAC, but produces a uniform increase at 2.0 MAC. Regional differences were noted at 1.5 MAC with increased flow to the cerebellar, limbic, and brain stem structures (23). The actual increase in intracranial pressure that such an increase in CBF will cause is determined by the brain compliance—the less compliant the system, the greater the increase in pressure.

A dose-related decrease in CMR_{O_2} is seen with all halogenated anesthetics until neuronal function ceases, as reflected by an isoelectric electroencephalographic tracing. This pattern is produced clinically with isoflurane at 2-MAC concentrations. Thus, an "uncoupling" of the CMR_{O_2}-CBF relationship occurs, which may represent a "resetting" in response to higher tissue P_{O_2} demand (15).

Other studies on the effects of isoflurane on cerebral metabolism have indicated that even at high inspired concentrations (6%), brain biopsies showed normal concentrations of ATP, ADP, AMP, normal phosphocreatine, and a normal energy change (24). The only change observed was a mild dose-related cerebral lactic acidosis which accompanied systemic acidosis.

The rate of production and absorption of cerebrospinal fluid (CSF) is a further determinant in maintenance of stability of intracranial dynamics. Nitrous oxide has little effect on either CSF production (V_f) or absorption (V_a) (25). However, both enflurane and ketamine have been shown to increase V_f and intracranial pressure markedly, for several hours (26). This effect may be the result of an action on choroid plexus metabolism whereby the metabolic rate for glucose is significantly increased. Halothane, which has no effect on choroid plexus glucose metabolism, decreases V_f by 30%, an action that does not change significantly with time (27). In a dog model, using the open ventriculocisternal perfusion method, there was no increase in CSF volume during prolonged isoflurane anesthesia (28), indicating little or no effect on V_f or V_a. The effect of narcotics on CSF production and absorption has not been well defined.

Thus, to summarize the effects of different anesthetic agents on CBF and hence on intracranial pressure, it appears that barbiturates and to a lesser extent, narcotics decrease cerebral metabolism and intracranial pressure by maintaining coupling of flow and metabolism, whereas inhalation agents, especially isoflurane, reduce metabolism but maintain or slightly increase flow, creating a "luxury perfusion" situation.

Electroencephalographic Changes

Seizures occur in approximately 14% of neurosurgical patients, who have not experienced attacks before surgery, in the first 24 hr following operation. If a seizure state preexists, attacks may be expected in as many as 35% of patients (29). As the increased cerebral activity and resultant hypoxia may prove devastating to a compromised brain, it is important to avoid any other factors that may contribute to a convulsive state.

There have been several reports of grand mal seizures following intravenous administration of as little as 100 μg of fentanyl (30). However, there has been no electroencephalographic documentation of seizures, and EEG studies during high-dose fentanyl have shown no abnormal cortical activity (31). But seizure activity can be produced experimentally by all narcotic analgesics at extremely high doses (31) (usually 100 times the anesthetic dose) and at lesser doses in subcortical structures (32). It has been suggested that rigidity is an explanation for the myoclonic movements associated with opiate anesthesia (33). Or the threshold convulsive dose of another drug, such as lidocaine, may be diminished by prior fentanyl administration (34).

Electroencephalographic, seizurelike abnormalities in humans have been reported during and following enflurane anesthesia, particularly in association with increasing depth of anesthesia and respiratory alkalosis (35). Although isoflurane, an isomer of enflurane, shares many of its physical properties, the effects on the EEG are those of dose-related decreases in activity.

At concentrations well below MAC, isoflurane increases electroencephalographic frequency from 8–12 Hz to greater than 15 Hz. Voltage increases as anesthetic concentration increases, and there is a progressive decrease in frequency and voltage until burst suppression occurs. No seizure activity is seen clinically during or following isoflurane anesthesia. Epileptic or spiking patterns do not appear, nor can they be evoked by hypocapnia, by increasing the anesthetic depth, or by auditory or visual stimuli (36). A recent report suggested that myoclonic and seizurelike activity might occur during general anesthesia with isoflurane. However, this patient also received two injections of fentanyl, 100 μg, as part of the anesthetic management. No electroencephalographic readings were reported (37). On the other hand, the effectiveness of isoflurane in the management of otherwise refractory status epilepticus has been described (38).

Systemic Effects

The characteristics of an ideal anesthetic pertain also for neurosurgical procedures. These factors include rapid onset of action and reversibility of effect, controllability of depth, easy administration, no organ dysfunction, no toxic metabolites, controllable elimination independent of hepatorenal function, pharmacokinetics unaltered by different physiognomy and age, high therapeutic index and specificity of action.

No such anesthetic exists.

Narcotic agents, specifically fentanyl, allow rapid induction of anesthesia. Duration of action and depth of anesthesia are less easily controlled, although continuous infusion of the newer agents allows better predictability, depending on pharmacokinetic recovery. Reversal of effect may be achieved by naloxone administration, although careful monitoring is necessary as the duration of effect of the latter is relatively short. Administration is technically easy, requiring only syringes and needles and, of course, venous access. Most of the new fentanyl family of opioids have little effect on cardiovascular or hepatorenal function, but cause profound respiratory depression. There is little change in neuromuscular transmission. Although potent opioids can produce a hemodynamically stable anesthetic induction, rapid administration can cause muscle rigidity. In one study, intracranial pressure increased rapidly with the onset of alfentanil-induced rigidity and returned to baseline when the rigidity was blocked by muscle relaxants. If hypercarbia develops because of inadequate mask ventilation due to the rigidity, intracranial pressure increases will be further exaggerated (39).

Opioid metabolites are essentially inactive and cause no organ damage. Hepatic degradation is necessary. Pharmacokinetic profiles of narcotics differ with age, sex, obesity, and drug history. Considerable drug interaction exists between tranquilizers, antidepressant agents, and narcotics. The new narcotics offer a high margin of safety.

Induction by inhalation agents, specifically isoflurane, is generally slower. However, duration of action and depth of anesthesia are more readily controlled, especially with time when a steady state of anesthesia has been achieved. Administration requires availability of a sophisticated delivery system to ensure accurate concentrations. At levels that provide surgical anesthesia, isoflurane causes little depression of myocardial function or tissue perfusion (40). Myocardial rhythm remains stable after exogenous administration of epinephrine (41). Baroreceptor activity may be well preserved, in contrast to the depression seen after barbiturate and halothane administration (42). Respiration is depressed in a dose-related fashion. Although all inhaled anesthetics are metabolized to some extent, only about 0.17% isoflurane is broken down, an amount that is probably clinically insignificant. Barbiturates and diphenylhydantoin, drugs commonly used for neurosurgical patients, increase microsomal defluorinase activity but cause little or no increase in isoflurane metabolism (43). Elimination is thus not dependent on kidney or liver function. The time course of the anesthetic effect is unaffected by altered body habitus. Postanesthetic complications are minimal.

Summarizing systemic effects as an indicator of choice of neuroanesthetic agents, it appears that although narcotics have a higher therapeutic index, easier mode of administration, and possibly less cardiovascular effects, these benefits are offset by respiratory depression and less flexibility in rapidly altering depth of anesthesia.

The analgesic effect of narcotics is usually supplemented by nitrous oxide. The gas, once thought to be completely safe, has been shown to have many adverse systemic effects, including alteration of intracranial dynamics by increasing CBF and metabolic rate and changes in the electroencephalographic pattern (20, 44). Use of nitrous oxide increases the incidence and severity of effects of air embolism and pneumocephalus (45).

Isoflurane, which has analgesic, anesthetic, and muscle relaxant properties, can be used as the sole agent for neuroanesthesia.

Specific Neuroanesthetic Procedures

Arterial Malformations. Occlusion of an intracranial aneurysm or arteriovenous malformation is often performed during periods of induced hypotension. Anesthesia with either fentanyl or isoflurane has been shown to preserve CBF during periods of trimethaphan hypotension more than if anesthesia is provided with N_2O. Isoflurane-treated animals exhibited no difference of CBF in cortical and subcortical structures between normotensive and hypotensive states (46). Studies during hypotension induced by 2-Cl-adenosine or deep isoflurane anesthesia showed brain oxygen tension values close to normotensive levels in the isoflurane group, but impaired in rats treated with adenosine, again indicating greater protection from isoflurane (47).

Occlusive Cerebrovascular Disease. Patients with cerebrovascular disease present several problems. They are frequently over 60 years of age, often suffer from hypertension and diabetes, and may have smoked heavily for many years. Often they receive three to six daily medications, including diuretics, antihypertensives, sedatives, anticonvulsants, anticoagulants, antidepressants, and insulin. Cardiac, respiratory, and renal disease may coexist. Wide fluctuations in arterial pressure and cardiac arrhythmias frequently complicate the anesthetic course. The neurosurgical procedure involves a potential period of cerebral ischemia during the vessel clamping required for carotid endarterectomy or during the cerebral vessel occlusion required for extracranial to intracranial anastomosis.

Ideally, the anesthetic agent must provide cardiovascular stability, minimal drug interaction or organ toxicity, compatibility with propranolol, brain protection by preservation of sufficient flow and decrease in CMR_{O_2}, maintenance of autoregulation, protected baroreflex action, and prompt return to consciousness. The patient should be able to breathe and cough effectively postoperatively. Early, accurate neurologic assessment is desirable. These objectives are probably better met by isoflurane than by fentanyl.

Tumors. Perhaps greatest controversy has arisen over the choice of anesthetic agents in patients with raised intracranial pressure associated with a tumor. Adams et al found no increase in lumbar cerebrospinal fluid pressure during isoflurane anesthesia in patients with intracranial mass lesions as long as hypocarbia at levels below 30 mm Hg was maintained (48). Campkin reported a decrease in intracranial pressure under similar circumstances (49). Preliminary data in our chronic hydrocephalic cat model indicate that isoflurane 2.5% has little effect on intracranial pressure or brain compliance if hypocarbia is maintained (50). However, Grosslight et al reported significant increase in intracranial pressure during isoflurane 1% administration in patients with tumors that had caused midline shift (51). The authors used nitrous oxide 70% in the study, a gas that has been shown to increase cerebral vasodilation during isoflurane anesthesia. Studies have shown that CBF increases caused by N_2O at a given MAC level are unrelated to the CBF prior to exposure to N_2O (44). Narcotic administration attenuates, but does not prevent, N_2O-induced cerebral vasodilation.

Certainly in surgery performed in the sitting position, nitrous oxide should be excluded. The use of nitrous oxide should be carefully considered in all cases of tumor extirpation. Below 1%, isoflurane has little or no effect on CBF. However, this concentration may be insufficient for adequate anesthesia in the absence of nitrous oxide. Thus, supplementation with a continuous infusion of fentanyl (1–1.5 μg/kg/hr) might be appropriate.

Stereotaxic Brain Biopsy. Precise intracranial placement of instruments to create a small lesion, obliterate a seizure site, or biopsy a tumor may require anesthesia of short duration, with no propensity for causing abnormal electrical activity or alteration of intracranial dynamics. Development of edema following production of a cryogenic lesion is less following intravenous anesthesia (barbiturates) than after isoflurane (52). In some centers, the most common reason for performing CT stereotaxic biopsies is in the diagnosis of toxoplasmosis associated with autoimmune deficiency syndromes. This disease is characterized by raised intracranial pressure. Anesthesia can usually be adequately managed by local infiltration and small incremental doses (25 μg) of fentanyl.

Head Trauma. Appropriate choice of anesthetic agent depends on the pathophysiology. We have demonstrated an improvement in the outcome of patients anesthetized with inhalation agents rather than with intravenous agents following blunt trauma (53). This may be related to improvement of cerebral blood flow by the inhalation agent in a disease state usually characterized by hypoperfusion. On the other hand, missile injuries or severe head injuries in children are often associated with increased blood flow and delayed increases in intracranial pressure and may be better managed by an intravenous technique. Certainly, in all groups, patients who received only N_2O fared significantly worse, perhaps because of drug-induced increase in both CMR_{O_2} and CMR glucose. A negative synergistic interaction between the gas and barbiturates has been described (54).

Thus, some means of determination of cerebral blood flow is indicated in order to make a rational choice of anesthetic agents. The ability to measure CBF is not generally available. However, an association between CBF and arteriovenous oxygen difference across the brain ($A\text{-}VD_{O_2}$) has been shown. Normal AVD_{O_2} values are 6–6.9 vol %. In hyperemic states, AVD_{O_2} decreases. As ischemia develops, AVD_{O_2} increases to as much as 9 or 10 vol %. Measurement of this parameter has been used to obtain an appropriate therapeutic balance between degree of hyperventilation and diuretic administration (55). Similarly, determination of a low value for AVD_{O_2} might indicate that an appropriate choice of anesthesia would be a barbiturate technique, whereas high values would point to the need for isoflurane to increase CBF.

Brain Protection. Many agents and techniques have been suggested as beneficial in affording protection against hypoxic cerebral insult. By its depressant action on cerebral cortical electrical activity and CMR_{O_2} isoflurane has been shown to be efficacious in hypoxemic and ischemic models (24). However, in other studies isoflurane pretreatment did not ameliorate postischemic neuronal necrosis in the rat (56). No decrease in neurologic deficit could be attributed to isoflurane in a baboon model of focal ischemia (57). In the last study, less damage resulted if thiopental was infused after the insult. However, no studies confirm that barbiturates provide protection after complete global ischemia (58). Probably other pharmacologic agents, such as Ca^{2+} channel blockers, offer greater promise for cerebral protection than the anesthetic agents.

Summary

The answer to the question "Is isoflurane best for the cerebral circulation?" is a qualified "Yes." The qualifying factor is the pathophysiology of the disease process. Under normal circumstances isoflurane has little effect on intracranial dynamics and few, if any, adverse systemic reactions. Arousal is prompt, with minimal postanesthetic effects. However, in critical situations, isoflurane may exert dose-dependent deleterious effects on cerebral and cardiac function. To minimize these complications, and to avoid the use of nitrous oxide in all neurosurgical patients, moderate concentrations (1%) of isoflurane may be combined with continuous low-dose infusion of a short-acting narcotic, such as fentanyl (1 μg/kg/hr).

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Hypoxic Pulmonary Vasoconstriction and Anesthetic Drugs

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Anesthesia is known to interfere with many of the body's homeostatic mechanisms; therefore the anesthesiologist's responsibilities include an awareness of these effects so that the most appropriate technique is selected for the particular situation.

It is well documented that general anesthesia may impair pulmonary gas exchange and that arterial hypoxemia may occur as a result. Nunn (1) studied factors influencing arterial oxygen tension (Pa_{O_2}) during halothane anesthesia with spontaneous respiration. He found a calculated shunt of 14% of pulmonary blood flow, as compared with a calculated shunt of 1% in normal conscious supine subjects measured using the same techniques (2). Nunn suggested that the large shunt observed during anesthesia was probably caused by perfusion of totally unventilated parts of the lung. Marshall et al (3) studied pulmonary venous admixture before, during, and after halothane-oxygen anesthesia in spontaneously breathing volunteers. Percentage pulmonary venous admixture (Qs/Qt %) was 4.4% before anesthesia, rising to 12.1% and 14.8% at 40 min and 3 hr into the anesthesia, respectively, and 6.5% and 5.2% at 40 min and 3 hr following the anesthesia. These workers (3) essentially agreed with Nunn (1) but also concluded that, in their study, the postoperative hypoxemia was due not to respiratory depression but principally to the residual effects of an increased percentage of venous admixture which had developed during anesthesia.

Studies have shown that all anesthetics are associated with alterations of lung mechanics, such as decreased compliance and functional residual capacity, and changes in the distribution of ventilation (4). Although these may contribute to the impaired gas exchange observed, they do not represent the whole answer, because identical changes in mechanics occur with both inhalational and intravenous anesthetic agents, yet impaired oxygen exchange has been shown only with the inhalational agents (5). This suggests that inhaled agents exert a special effect of their own, which tends to produce hypoxemia.

Because of this background, interest has been taken in regulation of the pulmonary circulation through a homeostatic mechanism called hypoxic pulmonary vasoconstriction (HPV), which normally diverts blood away from hypoxic regions of the lung and thereby optimizes the gas exchange function of the lung.

In this review I present a brief overview of HPV as a basic mechanism, discuss the effects of inhalational and intravenous anesthetic drugs on HPV, attempt to draw some conclusions as to how, if at all, our anesthetic practice should be modified, and look at one potential future development.

Normal Mechanism of Hypoxic Pulmonary Vasoconstriction

HPV was first described in 1942 by Von Euler and Liljestrand (6). They were studying the hemodynamic changes in the pulmonary circulation of the cat in response to changes in inspired gas mixture. They anesthetized cats with intra-

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venous chloralose and recorded systemic arterial blood pressure from one carotid artery and pulmonary arterial pressure via a cannula inserted directly into the pulmonary artery. The cats were studied during both spontaneous and positive pressure ventilation. It was found that when the cats breathed a mixture of 10.5% oxygen in nitrogen, an increase of the pulmonary artery pressure invariably occurred. This effect was not influenced by vagotomy or stellate ganglionectomy and was regarded as a direct effect of hypoxia on the lung vessels. Breathing 100% oxygen caused a distinct fall in pulmonary artery pressure. Von Euler concluded that the increased pulmonary artery pressure during hypoxia was due to a direct effect on the pulmonary vessels, thereby increasing the blood flow to better aerated areas of the lung, which led to improved conditions for utilization of the alveolar air.

Whereas Von Euler made both lungs hypoxic, others have studied the effects of the size of the hypoxic lung segment and the size of the hypoxic stimulus on perfusion pressure and on flow diversion. In one such study Marshall et al (7) prepared six pentobarbital-anesthetized dogs with endobronchial tubes and electromagnetic flow probes. The effects of changing inspired oxygen concentration were examined in test lung segments of different size corresponding to left lower lobe, left upper lobe lingula, left lung, right lung, right lung plus left lower lobe, right lung plus left upper lobe lingula, and whole lung. In each test, the rest of the lung received oxygen. HPV in the test segment was demonstrated by both increased perfusion pressure and diversion of blood flow away from the hypoxic test segment. Marshall et al found that pulmonary perfusion pressure changes increased with the size of the hypoxic test segment from 0 (smallest hypoxic segment) to approximately 2.2 times baseline for the hypoxic whole lung. Flow diversion, as a percentage of flow to the test segment under normoxic conditions, decreased with increasing size of the hypoxic test segment, from a maximum of 75% for very small segments, to zero when the whole lung was made hypoxic. Flow diversion percent increased linearly as alveolar oxygen tension ($P_{A_{O_2}}$) was decreased in the range of 130–28 torr. In both flow diversion and changes in perfusion pressure, Marshall et al found the response to HPV to be predictable, continuous, and maximal at a predicted $P_{A_{O_2}}$ of 30 torr (4% oxygen). Thus, HPV causes a rise in both perfusion pressure and flow diversion.

What is the stimulus for this and where does it act? This was studied in an in vitro preparation of isolated rat lungs, which were perfused and ventilated with separate control of alveolar and arterial P_{O_2}. With perfusion flow held constant, HPV was measured as changes in perfusion pressure. HPV was found to be a function of both $P_{A_{O_2}}$ and $P_{V_{O_2}}$, and the relationship could be expressed as if the two combined to give a single oxygen tension at the stimulus site ($P_{S_{O_2}}$) (8). The relationship could be expressed mathematically as

$$P_{S_{O_2}} = (P_{A_{O_2}})^{0.626} \times (P_{V_{O_2}})^{0.375}$$

The fundamental HPV-$P_{S_{O_2}}$ response is a sigmoid with a 50% response when both $P_{A_{O_2}}$ and $P_{V_{O_2}}$ are 30.3 torr, at which point $P_{S_{O_2}}$ is approximately 50 torr. For regions of the lung that are atelectatic, the stimulus for HPV is the $P_{V_{O_2}}$ (9). The response is believed to be accounted for by each smooth muscle cell in the pulmonary arterial wall responding to the oxygen tension in its vicinity. The exact mechanism of the response is yet to be determined.

How does HPV affect arterial oxygen tension? Clearly, if flow diversion occurs when part of a lung is made hypoxic, arterial P_{O_2} should be higher than if there were no HPV. The relationship between Pa_{O_2} and amount of lung made hypoxic (10) demonstrates that when little of the lung is hypoxic, HPV has little effect on Pa_{O_2} because in this situation, the shunt will be small. When most of the lung is hypoxic, there is no significant normoxic region to which the hypoxic region can divert flow, and then it does not matter, in terms of Pa_{O_2}, whether the hypoxic region has HPV or not. In the latter case, however, active HPV, by increasing pulmonary vascular resistance, will add to the problems of an already hypoxic heart.

When the amount of lung made hypoxic is intermediate, say 30%–70% of total lung, then there may be a large difference between the Pa_{O_2} to be expected with normal HPV as compared to that in the absence of HPV. This is the situation that obtains during one-lung anesthesia for thoracic surgery, and here active HPV can raise Pa_{O_2} from potentially dangerous low levels to higher and safer ones. Thus, during studies of one-lung ventilation, shunt through the nonventilated lung is usually 25% of the total cardiac output in contrast to the 40%–50% shunt that might be expected if blood flow to the collapsed lung continued as if to a ventilated lung (11).

This brief review of normal HPV has demonstrated the value of HPV as a homeostatic mechanism and how impairment of it may account for arterial hypoxemia.

Effects of Anesthetics on HPV

Inhalational Agents

Buckley et al (12) were the first to describe the effects of anesthetic agents on HPV. They studied dogs and found that N_2O increased the HPV response, but that halothane 0.5%, which had no significant effect on cardiac output, abolished it. They suggested a need for further clinical studies, and this suggestion was certainly followed up. There have been many subsequent studies of the effects of anesthetics on HPV. All manner of ingenious preparations and various species have been used for these studies, and the results have frequently been inconsistent. In a recent excellent review, Benumof (11) has classified the preparations used for these studies as in vitro, in vivo nonintact, in vivo intact, and human studies. This useful classification will be followed here.

In Vitro Preparations. The first extensive studies of the effects of inhalational agents on HPV were by Sykes et al (13, 14). They used isolated cat and dog lung preparations perfused at constant flow using a special perfusion circuit and found that the pressor response to hypoxia could be elicited for periods of up to 5 hr and that it was inhibited in a dose-related manner by halothane, trichlorethylene, and diethyl ether.

These results were also found by Bjertnaes (15), who used isolated rat lungs as a model and observed dose-related inhibition of HPV with N_2O, diethyl ether, halothane, and methoxyflurane.

Recently, Marshall et al (16) used a similar isolated rat lung model to study the effects of halothane, enflurane, and isoflurane on HPV. All three were found to depress HPV in a dose-related manner. The concentrations in MAC units (for rats) at which a 50% depression of HPV (ED_{50}) occurred were 0.47, 0.60, and 0.56 for halothane, isoflurane, and enflurane, respectively, and neither the ED_{50} values nor the slopes of the dose-response curves were significantly different. It was concluded that these halogenated agents inhibit HPV with essentially identical potencies.

In Vivo Nonintact Preparations. Benumof and Wahrenbrock studied the effects of the inhalational agents in a dog model in which the left lower lobe had been isolated for ventilation purposes (17). Electromagnetic flow probes were placed around the main and left lower lobe (LLL) pulmonary arteries, and pulmonary artery and left atrial pressures were measured directly. Using this model they examined changes in LLL blood flow in relation to total cardiac output, in response to ventilation of the LLL with normoxic and various hypoxic gas mixtures, with and without addition of inhalational anesthetics (18). Selective ventilation of the LLL with nitrogen alone caused blood flow to the lobe to decrease by 53%. Responses to LLL hypoxia were remeasured during administration of inhalational anesthetics at 1- and 2-MAC concentrations both to LLL and to the rest of the lung. It was found that isoflurane and fluroxene progressively inhibited, and at 2 MAC halved, lobar HPV. Nitrous oxide (0.3 MAC) caused slight but significant inhibition, whereas halothane and enflurane caused slight and nonsignificant changes in lobar HPV. The effects on HPV of whole-lung administration of anesthetics were almost identical to those obtained when administration was confined to the test lobe alone. It was concluded that nitrous oxide, isoflurane, and fluroxene locally inhibit HPV and thereby increase total venous admixture, whereas halothane and enflurane do not have this effect. Interestingly, in a more recent report from the same laboratory using the same model, other workers were unable to demonstrate inhibition of the HPV by isoflurane (19). No explanation was offered as to why these results differed from those found using the in vitro preparations (15, 16).

In Vivo Intact Preparations. Sykes et al (20, 21) used the intact dog model to study the effects of nitrous oxide and halothane on HPV. In this model, each lung was ventilated separately but synchronously, one with 100% oxygen and the other with a control or a test mixture. Differential lung blood flow was assessed by infusing ^{133}xenon into the inferior vena cava and measuring the mixed expired xenon concentrations emanating from each lung. In this study the ratio of blood flows between the two lungs was deemed equal to the ratio of xenon counts between the two lungs. Using this model, Sykes et al confirmed that N_2O inhibited HPV (20), but halothane in 0.5%–1.5% inspired concentrations had no apparent inhibitory effect (21).

These findings generally are in agreement with the in vivo nonintact findings, but differ from those of the in vitro studies. Thus, there appear to be discrepancies between the results obtained in the carefully controlled in vitro models and the less easily controlled in vivo models.

What Is the Site of Inhibition by Inhalational Agents? This has been addressed by Bjertnaes et al using the isolated rat lung preparation (22). They studied the reduction of a standardized HPV response during administration of halothane via (a) the airways; (b) the pulmonary artery, by normal anterograde perfusion of the preparation; and (c) the pulmonary veins by retrograde perfusion of the preparation. HPV was most effectively inhibited when the halothane was presented to the alveoli (via the airways), less when presented to the arterial, and least when presented to the venous segments of the pulmonary vasculature. It was therefore suggested that HPV is inhibited by halothane at some extravascular site on the arterial side of the pulmonary vasculature, functionally closer to the alveoli than to the responding vessels.

Intravenous Agents

Using the isolated, perfused rat lung model in which profound depression of HPV by inhaled agents was observed, Bjertnaes studied the effects of intravenous agents including fentanyl, pentazocine, ketamine, droperidol, diazepam, pentothal, and pentobarbital, administered via the perfusion circuit (15). When administered to result in clinically useful concentrations in the perfusate, none of these agents appeared to have any effect on HPV.

Because inhalational agents depressed HPV maximally when given via the airways (22), Bjertnaes et al decided to also test the effect on HPV of nebulized fentanyl administered via the airways as compared to via the perfusion circuit, in the isolated rat lung model (23). Once again, no inhibition of HPV was seen with the nebulized fentanyl given via the airways or via the perfusion circuit.

Lumb et al (24) used an intact dog (in vivo intact) model to compare shunt fractions (Qs/Qt%) during ketamine infusion with those during halothane anesthesia. They observed a consistently lower Qs/Qt% with ketamine infusion and considered that their model was adequate and that no additional factor could account for these differences. They concluded that ketamine resulted in better-maintained HPV than did halothane anesthesia.

Based on the overall results of the first three types of preparations (in vitro, in vivo nonintact, and in vivo intact), it is generally believed that inhalational agents inhibit HPV, whereas intravenous agents do not have this effect (25).

Human Studies

Human studies are perhaps the most significant because it is the application of our knowledge of HPV in patients that is of the greatest importance. However, these studies are obviously the most difficult to perform and to control for confounding variables.

Evidence from Perfusion Scans. In 1978, Bjertnaes used perfusion scans (scintigraphy) to assess the effect of inhalational agents on human HPV (26). He studied two groups of human volunteers who were undergoing surgery on the periphery (not abdominal or thoracic). The volunteers underwent arterial cannulation for monitoring of arterial blood gases, Pa_{O_2} in particular. Baseline Pa_{O_2}s were obtained with the subjects awake and breathing room air. Under intravenous anesthesia (pentothal, fentanyl, pancuronium), unilateral hypoxia was induced in the two groups of young men by ventilating one lung, the test lung, with N_2 and the other with O_2, using a double-lumen endobronchial (Carlens) tube.

In both groups the time period of unilateral hypoxia was divided into two sequences, one sequence with and one without inhalational anesthesia (halothane or diethyl ether). In 10 subjects (group A) inhalation anesthesia was administered during the second sequence, and in 7 subjects (group B) inhalation anesthesia was given during the first sequence. The blood flow distribution to the test lung during air breathing and following each of the two sequences of unilateral hypoxia was determined by lung scintigraphy. Thus, one lung was made hypoxic and Pa_{O_2}s were followed until they stabilized, at which time blood flow diversion as a result of HPV was thought to be maximal and steady. An intravenous injection of isotopically labeled albumin was made so that the macroaggregates would be distributed to and trapped in the lungs, according to the differential pulmonary blood flow. The inhalational agent was then introduced (group A) or withdrawn (group B) and the Pa_{O_2}s followed until another steady state was reached.

At this time a second injection of macroaggregates, labeled with a different isotope, was made so that subsequent scanning could provide information on pulmonary blood flow distribution at both times of interest. In group A the median test lung blood flow distribution decreased from 49% of total pulmonary blood flow (both lungs, room air) to 25% (i.v. anesthesia, unilateral hypoxia). After ipsilateral inhalational anesthesia was superimposed, flow increased to 34% of total pulmonary blood flow. The increase was significant for both the diethyl ether and halothane subgroups. Blood flow distribution to the test lung during the first period of unilateral hypoxia was significantly higher during diethyl ether or halothane administration (group B) than during the administration of intravenous anesthesia alone (group A). The damping effect of inhalational anesthetics on the response to hypoxia was observed at clinically used blood concentrations of these agents. It was concluded that diethyl ether and halothane inhibit HPV in humans and that this contributes to the development of arterial hypoxemia during anesthesia. The perfusion scans obtained during the various stages of this study appear to provide fairly convincing evidence that HPV occurs in humans.

One-Lung Anesthesia. Perhaps the greatest test of HPV in humans is seen in patients undergoing one-lung anesthesia for thoracic surgery. Here, the target lung is collapsed (as opposed to being ventilated with N_2) and the other lung is ventilated. Several studies have attempted to draw conclusions about the effects of anesthesia on HPV from the one-lung-anesthesia situation.

Weinreich et al (27) used a continuous infusion of ketamine in 110 patients undergoing one-lung anesthesia. They theorized that because it has positive effects on the cardiovascular system and is an intravenous agent with no inhibitory effect on HPV, it would produce improved oxygenation in such patients. They found that none of their 110 patients had a Pa_{O_2} of less than 70 torr when FI_{O_2} was 1.0, as compared to other studies (28, 29) in which halothane was used, where 15%–25% of patients had a Pa_{O_2} of <70 torr with an FI_{O_2} of 1.0. Weinreich et al had no control group of their own, but suggested that ketamine provided a satisfactory alternative to the volatile agents for one-lung anesthesia in patients in whom relative hypoxemia might be unacceptable during the operation.

Following up on the last study, Rees and Gaines (30) compared a ketamine-oxygen technique with an enflurane (1%–3% inspired concentration)-oxygen technique in 24 patients undergoing one-lung anesthesia. They compared Pa_{O_2} and Qs/Qt% in the two groups of 12 patients studied. They reported no statistically significant differences in Pa_{O_2} or Qs/Qt%, between the two groups, but stroke volume index, left ventricular stroke work index, and cardiac index were significantly greater with ketamine. These findings suggested that ketamine afforded no advantage over enflurane anesthesia in terms of Pa_{O_2} and Qs/Qt% during endobronchial anesthesia, in contrast to the suggestion of Weinreich et al (27).

Recently, Rogers and Benumof (31) reported a study during one-lung anesthesia designed to settle the question of intravenous versus inhalational agents during these procedures. They postulated that if inhalational anesthetics significantly inhibit HPV in humans, and all other factors that might influence Pa_{O_2} remain "relatively constant," then the administration of inhalational anesthetics during one-lung ventilation should decrease Pa_{O_2}. They tested this hypothesis by measuring Pa_{O_2} before, during, and after the administration of halothane or isoflurane to 20 intravenously anesthetized patients requiring thoracotomy and one-lung ventilation. Ten patients received halothane and 10 isoflurane. Within each of these two groups, 5 patients received ketamine and 5 methohexital as the intravenous anesthetic.

The study involved five stages:

1. Two-lung ventilation, intravenous anesthesia.
2. One-lung ventilation, intravenous anesthesia.
3. Discontinue intravenous agent, start inhalational agent, one lung ventilation.
4. Discontinue inhalational agent, restart intravenous agent, one lung ventilation.
5. Two-lung ventilation, intravenous anesthesia.

The results showed no significant differences between stages 2 and 3, or 3 and 4, in Pa_{O_2} in both halothane and isoflurane groups. There was, however, a small but not statistically significant decrease in both cardiac index and pulmonary artery pressure with the administration of the inhalational agents, in both the halothane and isoflurane groups.

These authors considered that other variables tending to affect Pa_{O_2} remained "fairly constant" throughout and concluded that the inhalational agents at about 1-MAC concentrations do not significantly affect HPV in humans. They attributed differences between their results and the large number of previous animal studies, which had arrived at conclusions opposite to theirs, to the use of different species and different methodologies.

Marshall, however, commented recently that the contrast between the in vitro and the in vivo studies is sufficiently striking to suggest that other variables are obscuring the effects of inhibition of HPV in the in vivo studies (32). One such variable is cardiac output, which is altered to a markedly different extent by different inhalational agents. Marshall collected data from a large number of published studies and plotted the HPV ratio (% flow to hypoxic segment with anesthetic/% flow without; the ordinate) against cardiac output ratio (cardiac output with anesthetic/cardiac output without; the abscissa) measured at the same time. The regression line drawn through these points showed:

$$\text{Anesthetic action on HPV ratio} = 0.46 + 0.83 \times (\text{cardiac output ratio})$$

The correlation coefficient was highly significant ($r = 0.7$).

The relationship reveals that in the presence of inhalational anesthetics, the effectiveness of HPV varies inversely with cardiac output. Thus, during the administration of halothane, a direct inhibition of HPV by the agent may be offset by the enhanced responsiveness accompanying decreased cardiac output, with the result that flow diversion and gas exchange (as assessed by Pa_{O_2}) and, by inference, HPV may all appear to be unaffected.

This HPV-cardiac output relationship therefore provides a reasonable explanation for some of the discrepancies between the in vivo and in vitro studies, and for why no differences are apparent between the effects of intravenous and inhalational agents during one-lung anesthesia in the human studies. Indeed, an increase in cardiac output as occurs with some of the intravenous agents might even be construed as being detrimental to the normal HPV response, and it could be argued that these agents should be avoided because of their indirect damping effect on HPV. Clearly, many other important variables have an influence on arterial oxygenation and have to be considered before the inhalational or intravenous agents are either praised or condemned.

Potentiators of HPV

Whereas in the past most research efforts have been directed to studying inhibition of HPV, newer research has investigated potentiators of this response. Such potentiators might then have a role in the management of patients who develop hypoxemia under anesthesia.

Almitrine, a respiratory stimulant drug, has been found to improve Pa_{O_2} in patients with chronic obstructive pulmonary disease, and to have this effect even in the absence of ventilatory stimulation (33, 34). It has recently been shown to potentiate HPV in intact dogs anesthetized with pentobarbital (35). Another study in thoracotomized dogs failed to demonstrate such potentiation (36). This failure, however, may have been due to the fact that the dogs in the latter study already had a maximal HPV response prior to the administration of almitrine.

Prostaglandins have been suggested as having a role in HPV inhibition. Prostaglandin inhibitors have therefore been investigated for use as potentiators of HPV. Recently, ibuprofen, a cyclooxygenase inhibitor, was found to potentiate HPV in a hypoxic isolated rat lung preparation, and to reverse the inhibition of HPV caused by 0.5-MAC halothane in the same preparation (37).

Summary

Hypoxic pulmonary vasoconstriction is a fascinating mechanism but is difficult to study, particularly in humans. From this brief overview, several points may be drawn.

1. HPV does exist and is a useful homeostatic mechanism.
2. HPV means different things to different people. Essentially it is vasoconstriction, which may cause flow diversion and perfusion pressure changes, which may in turn cause changes in arterial oxygenation. Depending on the point in the sequence one is looking at, conclusions on the effects of an agent or other maneuver on HPV may vary.
3. HPV is not directly inhibited by intravenous agents.
4. HPV is directly inhibited by inhalational anesthetics. Because of compensatory mechanisms, which may be difficult to measure accurately, particularly in the intact human model, the inhibition usually—though not always—is of no clinical consequence.
5. Present consensus is that inhalational agents are not contraindicated for procedures such as thoracic surgery requiring one-lung ventilation. Indeed, some advocate their use on the basis of a salutary effect on bronchomotor tone, ability to use high FI_{O_2}s, few negative cardiovascular effects, and rapid elimination (11). However, there may be some patients, particularly those with generalized lung abnormalities, in whom unexpected hypoxemia occurs, and in these patients change to an intravenous agent should be considered.
6. Potentiators of HPV are still at the experimental stage. However, as more is learned about the biochemical mechanisms of HPV, potentiators may become a real therapeutic modality for patients who develop hypoxemia during anesthesia.

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Protamine Administration: Untoward Responses and Their Mechanisms

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Protamine is a drug used to reverse heparin anticoagulation after hemodialysis, cardiopulmonary bypass, vascular surgery, and cardiac catheterization, and to prolong the absorption of subcutaneously injected insulin. It is a polycationic peptide that is 67% arginine. These positively charged arginine moities give protamine its basic properties. Conversely, heparin is a polyanionic mucopolysaccharide. Together heparin and protamine can electrostatically bind to create a stable macromolecular complex.

Clinical problems associated with administration of protamine stimulated avid research into the mechanism behind the observed hemodynamic effects.

Animal Studies. In dogs, investigators found that protamine administration was associated with a fall in systemic arterial pressure, and numerous etiologies were suggested to explain the hypotension. Goldman et al reported that protamine administration resulted in a fall in femoral arterial pressure and left ventricular end-diastolic pressure (1). There was also a concomitant increase in pulmonary arterial pressure and central venous pressure. It is noteworthy that these changes occurred in heparinized and nonheparinized animals, but the changes in the nonheparinized animals were slightly less profound. Similar hemodynamic results were obtained by Radegran and McAslan (2), who also noted that the effects of protamine administration were inhibited by acetylsalicylic acid. Fadali et al studied heparinized dogs and noted a significant drop in femoral arterial pressure after protamine administration (3). In their model, the lungs were bypassed and the proposed etiology of hypotension was a direct negative inotropic effect. In contrast, Gourin et al found that protamine decreased systemic vascular resistance, and when filling pressure and heart rate were controlled, it did not affect contractility (4). Thus, a multitude of hemodynamic changes have been described after protamine administration under various study conditions.

Although Goldman et al found that protamine administration altered the hemodynamics whether or not heparin was present (1), Stefaniszyn et al found that no hemodynamic alterations occurred during protamine administration unless the animal was heparinized (5). Thus, it is not clear whether it is protamine or the heparin-protamine complex that causes the hemodynamic effects. Recently, Fiser et al reported another variable factor (6). They compared the hemodynamic effects of protamine administration in swine. Some animals received no heparin and others were heparinized with either beef lung or pork mucosal heparin. Protamine alone caused no significant changes. Protamine administration in beef lung-heparinized swine resulted in a gradual, but modest, increase in mean pulmonary artery pressure without other hemodynamic abnormalities. In contrast, protamine administration in pork mucosal-heparinized animals resulted in a rapid profound increase in pulmonary arterial pressure and pulmonary vascular and systemic vascular resistances, along with a marked drop in cardiac index. Fiser et al con-

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cluded that the type of heparin administered played a significant role in the response to protamine administration and that heparin is required to produce significant hemodynamic changes.

Prospective Human Studies. Prospective human studies have also yielded variable results. Conahan et al rapidly infused protamine after cardiopulmonary bypass and found no hemodynamic consequences (7). Conversely, Jastrezebski et al reported a transient fall in mean arterial pressure and a prolonged increase in pulmonary arterial pressure (8). Shapiro et al (9) and Michaels and Barash (10) also noted a drop in mean arterial pressure after protamine administration, but in their studies this drop was secondary to a marked decrease in systemic vascular resistance. Patients with poor left ventricular function (preoperative ejection fraction less than 40%, cardiac index less than 2 liters/min, or an elevated PCWP) have been particularly susceptible to a drop in mean arterial pressure, owing to their inability to increase cardiac index and compensate for the decreased systemic vascular resistance.

Clinical Problems

In addition to the prospective studies, numerous case reports of severe reactions to protamine have appeared in the literature. These idiosyncratic reactions can be divided into two types: immunologic phenomena and catastrophic pulmonary hypertension.

Immune Reactions. The immunologic reactions are characterized by profound circulatory shock, bronchospasm, capillary leak, and urticaria. Although these reactions are very rare, three groups are at increased risk: (a) patients with fish allergies, (b) NPH insulin-treated diabetics, and (c) patients who have had a vasectomy.

Several reports have appeared in which a patient with a history of an allergic reaction to fish had an untoward response to protamine. Commercially available protamine is derived from salmon sperm, and there is a potential for cross-reactivity to the fish antigens. In one report a patient had a positive skin test to protamine, elevated IgE, and a codfish allergy documented by radioallergosorbent testing (11). Fish and shellfish are phyllogenetically different, and no reports of a shellfish allergy and an adverse reaction to protamine have appeared.

Insulin-dependent diabetics also appear to be at risk for major protamine reactions. It is likely that the subcutaneous injection of small doses of protamine has sensitized these patients to relatively large intravenous doses. Stewart et al studied 651 consecutive patients undergoing cardiac catheterization who received protamine (12). Seven patients experienced a major reaction that required catecholamine treatment. Four of the patients who reacted were NPH insulin-dependent diabetics, an incidence of 27% (4/15). In contrast, only 3 patients who never received NPH insulin reacted, an incidence of 0.5% (3/636); one of these patients had a history of an allergy to fish. The authors concluded that the fiftyfold increase in major reactions to protamine in insulin-dependent diabetics warranted avoidance of protamine or, if necessary, extremely cautious administration of protamine to these patients.

No report of a protamine reaction in a patient who has had a vasectomy has appeared, yet this group is theoretically at risk. After vasectomy, sperm containing protamine are absorbed into the bloodstream, and 22% of the patients develop antibodies to human protamine. There is the potential for cross-reactivity between human and salmon protamine. As the group of vasectomy patients ages and requires invasive medical treatment with protamine administration for heparin reversal, this risk may become significant.

In these three groups of patients the role of heparin in the untoward response has not been clarified. Since some of the patients have positive skin tests to protamine alone, it may be assumed that these reactions to protamine are heparin-independent.

Catastrophic Pulmonary Hypertension. The second type of idiosyncratic reaction that has been reported is catastrophic pulmonary hypertension. Lowenstein et al reported 5 such cases in patients with preexisting pulmonary hypertension (13). In all 5 cases, the pulmonary hypertension was associated with right-heart failure (elevated central venous pressure) and with decreased left atrial and systemic pressures. These reactions occurred after minimal doses of protamine and required pharmacologic intervention.

Postulated Mechanisms

Vasodilation. Many investigators have sought to define the mechanisms of these protamine reactions. Jones et al postulated that protamine, a positively charged molecule, may bind calcium (14). The acute reduction in ionized calcium could then explain the observed hypotension. To test their hypothesis, they measured ionized calcium levels before and after protamine infusion. Although they observed a 10% reduction in ionized calcium after protamine infusion, they felt that this small change was insufficient to explain the observed hemodynamic effects.

Another potential mechanism of vasodilation is histamine release. Fadali et al found no change in the response to protamine infusion in histamine-depleted animals (3). Conversely, Stoelting et al found that rapid administration of protamine led to hypotension and increases in the level of circulating histamine (15). Blockade of serotonin, another vasodilator, by methylsergide prior to protamine infusion did not alter the observed hemodynamic effects (2).

Thus there does not appear to be a clear mechanism for the observed vasodilation with protamine administration.

Immune Phenomena. Two potential mechanisms may explain the immunologic phenomena: anaphylactic and anaphylactoid reactions. The two are clinically indistinguishable, but are discernible by serologic testing. Anaphylactic reactions are antibody-mediated and anaphylactoid reactions are not.

The anaphylactic reactions are either Coombs and gel classification system type I or type II. Type I reactions are IgE-mediated, and the patients often have a positive skin test to the antigen. The antigen and the antibody stimulate mast cells and basophils to degranulate. Numerous mediators of anaphylaxis are released, including histamine, eosinophil chemotactic factor A, slow-reacting substance of anaphylaxis A, kinins, prostaglandins and thromboxane, and platelet-activating factor. Histamine causes puritius, vasodilation, bronchospasm, and capillary leak. Eosinophil chemotactic factor A attracts eosinophils. These cells degranulate and liberate enzymes that break down the active mediators that help to maintain homeostasis. Slow-reacting substance of anaphylaxis A is a combination of leukotriene C_4, D_4, and E_4. These are products of the lipoxygenase pathway of arachadonic acid, and they can cause bronchoconstriction, coronary vasoconstriction, decreased inotropy, chemotaxis, and cellular injury. The prostaglandins and thromboxanes are cyclooxygenase products of the arachadonic acid pathway. Prostaglandins are vasodilatory, and thromboxanes are vasoconstricting, platelet aggregatory, and produce capillary leak. The Coombs and gel type II reactions are IgG- or IgM-mediated. The antibody-antigen complex stimulates complement activation and the liberation of anaphylatoxins $C3_a$ and $C5_A$. These compounds have chemotactic properties and cause mast cell and basophil degranulation. The same vasoactive substances as with a type I reaction are liberated, and a similar clinical picture appears.

Anaphylactoid reactions occur when complement is activated by a means other than antibody mediation. Chenoweth et al have demonstrated that complement is activated at the end of cardiopulmonary bypass (16). Usually the level of complement activation is not sufficient to cause a major reaction. Heparin and protamine form a macromolecular complex with a geometry similar to an antibody-antigen complex, and this complex has been shown to stimulate complement activation (17). In some patients, this additional complement activation may cause clinical problems. In sheep, MacDonald et al have shown that activated complement stimulates thromboxane synthesis and pulmonary hypertension results (18). Furthermore, pretreatment with aspirin, a cyclooxygenase inhibitor, prevents the rise in thromboxane and the associated pulmonary hypertension. Similar events may occur in humans and create catastrophic pulmonary hypertension.

In conclusion, protamine is a drug commonly administered in the operating room. Although it is frequently harmless, it may precipitate many potential problems. With a better understanding of the mechanisms of these untoward responses, clinical care should improve.

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Cardiovascular Effects of Anesthetics in the Neonate

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The cardiovascular effects of anesthetic agents in neonates represent the interaction of the primary effect that these agents have on the cardiovascular system with the neonatal heart and circulation, which is still undergoing development and has not yet reached maturity. Much of the information we have gained about these interactions comes from observations in human neonates, as well as from laboratory studies of newborn animals.

Developmental Cardiovascular Physiology

Before individual anesthetic agents are considered, it is worthwhile reviewing what is known about developmental cardiovascular physiology. Friedman has shown that both length-tension and force-velocity curves in fetal sheep are markedly different from those generated in adult sheep (1). When active length-tension curves were examined, fetal myocardium generated significantly less tension than did adult myocardium. This discrepancy between fetal and adult muscle was most marked at $L_{\max}$, the maximum resting length of the muscle strip. Conversely, when passive length-tension curves were examined, fetal muscle was found to generate higher tension than that in the adult muscle at any given length, and the discrepancy was once again greatest at $L_{\max}$.

We can conclude from these studies that ventricular compliance is decreased in fetal myocardium compared to adults, and the differences are most marked at $L_{\max}$. Decreased compliance has also been shown in sheep at 1 and 3 weeks of age compared to adults (2). In this group of animals, left ventricular end-diastolic pressure was raised to 20–25 mm Hg by volume infusion. As left ventricular end-diastolic pressure rose above 15 mm Hg, left ventricular stroke work decreased in the 1-week-old sheep but not in the other animals. As left ventricular end-diastolic pressure rose above 6–10 mm Hg, the velocity of circumferential fiber shortening also decreased in the youngest animals. Total peripheral resistance decreased as left ventricular end-diastolic pressure rose in the older animals. This was in contrast to the 1-week-old animals, in which total peripheral resistance did not change as end-diastolic pressures increased.

Thus we have evidence that the newborn ventricle is compromised in two ways: (a) decreased compliance compared to adults, and (b) a lack of decrease in afterload as left ventricular end-diastolic pressures are increased.

At a microscopic level, it has been shown that individual myofilaments of cardiac muscle generate similar forces in both fetal and adult heart (1). The length of the sarcomere at $L_{\max}$ is also the same in both groups, having an average length of 2.18 μm. However, fetal and adult tissue differ markedly in that the proportion of contractile mass to total tissue is much greater in adult than fetal tissue. Adult myocardium contains approximately 60% contractile tissue, whereas the fetal heart contains only about 30% contractile tissue. This difference in contractile mass can explain the differences in extent of

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shortening and velocity of shortening that are seen at any given tension when fetal tissue is compared with adult tissue.

The right ventricle is the main pumping chamber for the systemic circulation in utero, and it is a thicker and less compliant ventricle than the normal adult right ventricle. After birth, the left ventricle takes over as the systemic ventricle and rapidly becomes thick-walled and less compliant. The left ventricle takes on adult characteristics at a faster rate than the right ventricular wall thins and becomes more compliant. With an intact pericardium, the right and left ventricular volumes are interdependent. Thus, in the neonatal period, the filling of one ventricle (the left) will reduce the distensibility of the other ventricle (the right). This interference of one ventricle with the filling of the other is most pronounced in the fetal heart. Ventricular distensibility is greatest in the adult, less in infants, and least in newborns (1).

Rudolf has demonstrated that the developing heart appears to have a rate-dependent cardiac output. Because of limited compliance, the ability of the developing ventricle to increase stroke volume is limited as heart rate decreases (3).

At birth, parasympathetic innervation appears to be dominant. When newborn hearts are treated with either atropine or propranalol, the heart rate increases to a much greater extent (30%–50%) with atropine than the decrease with propranalol (6%–10%) (4).

In fetal and newborn hearts most norepinephrine present appears to be in preterminal nerve trunks and not in finely arborized nerves in close proximity to adrenergic receptors. This developmental "denervation" in the perinatal period may account for the increased sensitivity of fetal and newborn muscle to exogenous norepinephrine (5).

Finally, in both newborn sheep and rabbits decreased baroreceptor sensitivity has been demonstrated (6–9).

Effects of Halothane

The depressant effects of halothane on the heart in children have been demonstrated by both McGregor et al and Barash et al (10, 11). Using echocardiography, Barash et al were able to demonstrate depression of cardiac output, ejection fraction, and velocity of circumferential fiber shortening at increasing concentrations of halothane. When heart rate was increased with atropine, cardiac output could be raised to levels greater than control values. Velocity of circumferential fiber shortening could also be improved by atropine and with the sympathetic stimulus induced by tracheal intubation. No differences have been demonstrated between enflurane and halothane in terms of their myocardial depression in children.

Friesen and Lichtor examined the effects of halothane on blood pressure and heart rate in infants less than 26 weeks of age (12). Three groups of infants were studied. The first received halothane in increasing concentrations up to 3% (inspired). The second group received atropine approximately 40 min prior to anesthetic induction with similar concentrations of halothane as seen in the first group. In the third group halothane concentration was limited to 1.25% (inspired), and intramuscular succinylcholine was administered to facilitate tracheal intubation. The decrease in heart rate was 30% in group 1, 18% in group 2, and 29% in group 3. The decrease in mean arterial pressure was 54% in group 1, 44% in group 2, and 40% in group 3. The lowest mean systolic blood pressures observed were 50 mm Hg (group 1), 65 mm Hg (group 2), and 69 mm Hg (group 3). However, the preinduction blood pressures seen in these infants were higher than those published either as normal data or as controls presented in other studies, and thus the percentage decrease in blood pressure reported may be artifactually large (13, 14).

One can conclude from these studies that halothane may in fact be associated with myocardial depression in concentrations high enough to perform endotracheal intubation. These studies, although demonstrating significant decreases in blood pressure, and presumably significant drops in cardiac output, do not provide information on possible compromise of tissue oxygenation.

Similar decreases in heart rate and blood pressure have also been shown to occur during inhalation induction in infants less than 6 months of age with isoflurane (15). As with halothane, heart rate can be maintained to a better extent when atropine is administered prior to induction.

Gregory examined the depressor baroreceptor response in premature infants undergoing patent ductus arteriosus ligation during halothane anesthesia (16). These children received halothane (0.5%–1% inspired) as their primary anesthetic and did not receive atropine. During ductal ligation the systemic arterial pressure usually rises suddenly at the moment when the ductus is tied. If the depressor baroreceptor response were intact, one would expect heart rate to decrease as the blood pressure suddenly increases. This was not observed in these infants, leading Gregory to conclude that the baroreceptor responses were obliterated by halothane in this group of premature infants.

In attempting to further understand the myocardial depressant effects of halothane, Cook et al examined the concentration of halothane in cardiac tissue of rats at varying ages (17). The concentration of halothane in myocardial tissue was measured at anesthetic concentrations, and at concentrations producing cardiac failure. The ratio of halothane concentration at cardiac failure divided by the halothane concentration at anesthetic concentrations was calculated for each population. The youngest rats had a lower ratio compared to older rats, and in absolute terms the cardiac concentration of halothane at the point of cardiac failure was approximately half that found in older rats. Thus, the younger animals appeared to be less tolerant of halothane than older animals.

Effects of Other Anesthetics

Fentanyl. Fentanyl has been advocated as the primary anesthetic agent for patent ductus arteriosus ligation in premature infants by Robinson and Gregory (18). Fentanyl, 30–50 mg/kg, was used in conjunction with pancuronium and air/oxygen. No significant changes were noted in heart rate or blood pressure. In another study of premature infants undergoing patent ductus arteriosus ligation, fentanyl, 30 mg/kg, was also administered (19). Here, however, there was a gradual increase in the heart rate between the time of skin incision and the time of skin closure. There were no significant changes in blood pressure.

Nondepolarizing Muscle Relaxants. The nondepolarizing muscle relaxants differ mainly in their effect on heart rate and blood pressure (20). Pancuronium and gallamine have the ability to increase heart rate and blood pressure, whereas curare, metocurine, vecuronium, and atracurium have no significant effects on these cardiovascular variables in neonates. The tachycardia associated with gallamine appears to be greater than that seen following pancuronium.

Succinylcholine. Cook et al have reported the development of pulmonary edema in three infants following the use of intramuscular succinylcholine (21). The mechanism by which succinylcholine might alter pulmonary vascular tone or permeability is unclear. This phenomenon has not been reported after the use of intravenous succinylcholine.

Summary

Most of the significant differences between the neonate and the adult with respect to anesthetic effect can be traced to developmental immaturity and the transition from a fetal pattern of circulation to a normal adult pattern. Because of different rates of maturation even in normal neonates, one should expect wide variations in dose-response relationships in this age group, and in fact, this does occur.

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Anesthesia for the Aged: Some Pharmacokinetic and Pharmacodynamic Considerations

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The number of very elderly patients subjected to anesthesia continues to increase as the population ages. At The Mount Sinai Medical Center, 147 patients aged 90 years or more underwent 171 surgical procedures during the 5-year period 1970–1974 (1). For the first 5 years of the 1980s the number increased to 254 patients undergoing 270 procedures.

The problems associated with anesthesia for the aged largely relate to the well-recognized altered physiologic status and concomitant pathologic conditions common to elderly patients. However, the selection of anesthetic drugs and agents for the aged has usually been based on an appreciation of the systemic effects of anesthesia in younger persons.

Recently the importance of the pharmacokinetic consequences of physiologic changes in the elderly has become appreciated. Such changes (Table) are well known, but few drugs of anesthetic interest have been extensively studied in the elderly with respect to pharmacokinetic or pharmacodynamic effects. It is, however, generally appreciated that the aged show a greater response to central nervous system depressants, less of a response to central nervous system stimulants, and paradoxical responses to certain agents, and have a higher incidence of adverse reactions due to drug interactions or altered physiologic responses. Whether the primary mechanism of altered drug effect in the aged is due to pharmacokinetic or pharmacodynamic factors remains, with most agents, largely unknown.

Induction Agents

The clinical impression that the elderly are more sensitive to thiopental is supported by several recent studies demonstrating that the thiopental dosage needed for induction of anesthesia decreases with age.

Christensen et al (2) found that the increased sensitivity of the aged was due to changes in the initial distribution kinetics of thiopental rather than alterations in total distribution volume and elimination. They found that the volume of distribution and terminal half-life increased, but the increased sensitivity to thiopental was due to a reduced rate of distribution from the central compartment to fast equilibrating peripheral compartments. The induction dose for patients aged 60–79 years was 70% of that required for patients aged 20–40 years.

A strong correlation between age and the apparent volumes of distribution was found by Jung et al in a study of 22 female patients aged 25–83 years (3); the increase in elimination half-life with age was primarily a function of volume of distribution. No relationship was found between age and volume of the central compartment. In this study there was an increase in the free fraction of thiopental with age, which was not related to the concentration of serum albumin or serum protein and therefore was independent of protein binding.

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TABLE

Pharmacokinetic Effects of Physiological Changes in the Aged

Physiologic change	Pharmacokinetic effect
Increased circulation time Decreased cardiac output	Delayed onset, prolonged effect
Decreased lean body mass Decreased body water Increased body fat	Changes in distribution
Decreased serum albumin	Reduced binding
Decreased liver Mass Blood flow Enzyme activity	Reduced metabolism, detoxification
Decreased renal Mass GFR Tubular secretion	Impaired elimination
Decreased metabolic rate	Delayed elimination

Homer and Stanski (4) found that the dose of thiopental required to produce burst suppression on the EEG decreased significantly and linearly with age; for each decade increase in age, the dose decreased by 1 mg/kg. These workers chose the EEG measurement of leading spectral edge as an objectively quantifiable index of anesthetic drug effect and found that the biophase thiopental concentration required to produce 50% of maximal EEG slowing is not affected by age. It therefore appears that the aged brain is not sensitive to the EEG effects and presumably anesthetic effects of thiopental.

Homer and Stanski found that the volume of the central compartment was reduced in the elderly and that thiopental had a smaller initial distribution volume. Elderly patients developed adequate serum levels to produce burst suppression sooner than younger patients and hence had a decreased dose requirement. In this study there was little change in protein binding or elimination half-life. Such findings with respect to changes in the volume of the central compartment with age are controversial (5). However, the reduced thiopental dosage requirement of the elderly does appear related to a change in early drug distribution rather than to total distribution volume and clearance. The dose requirement of thiopental changes with age, but there is no increase in brain sensitivity to the drug (4).

The reduced dose requirements of benzodiazepines in the elderly may also be related to pharmacokinetic factors. Alterations in volume of distribution and clearance with age have been demonstrated with midazolam (6, 7). The short elimination half-life of midazolam, approximately 2 hr, is markedly prolonged in the aged (7). In general, the benzodiazepines may produce prolonged effects in the elderly.

Muscle Relaxants

Long-acting muscle relaxants, such as curare and pancuronium, depend initially on redistribution and ultimately on urinary excretion for elimination. These agents have a prolonged duration of action in the aged related to decreased lean body mass and reduced renal function.

Duvaldestin et al (8), studying pancuronium, found the elimination half-life greatly prolonged in the elderly. The delay in plasma concentration decay and prolongation of duration of action was due to delayed elimination. The dose response and plasma concentration response relationships to pancuronium were not affected by age. It appears that the prolonged effect of pancuronium in the aged is related to a reduction in urinary excretion and that the pharmacodynamics of pancuronium do not change with increasing age.

Pharmacokinetic factors are also responsible for the prolonged response to *d*-tubocurarine and metocurine in the elderly. Matteo et al (9) found that plasma clearance, initial volume of distribution, and volume of distribution were reduced with these agents and elimination half-life prolonged. Plasma concentrations of *d*-tubocurarine were higher in the elderly, even up to 24 hr, when compared to younger controls. The sensitivity to *d*-tubocurarine and metocurine did not alter with age; there was no difference in the log plasma concentration twitch response relationship, between 20% and 80% paralysis, in the aged and younger patients (9). The dose requirement of vecuronium is also reduced in the aged (10).

Atracurium appears to be a useful muscle relaxant for the aged; the dose requirement and recovery time with this agent are not age-related (11). The processes responsible for inactivation of atracurium, Hoffman elimination and plasma hydrolysis, presumably are well maintained in the aged and effectively compensate for the impaired regulatory functions in the aged usually responsible for delayed elimination of other nondepolarizing muscle relaxants.

Narcotics

Because the opiates and their synthetic analogs in general lack the direct cardiovascular depressant effects of volatile inhalation agents, they have been widely used for older patients. However, the aged appear more sensitive to these agents. The elimination half-life of morphine is greately prolonged in the aged. The myocardial depression and tachycardia associated with meperidine are major hazards in the elderly. Fentanyl, a short-acting narcotic, produces little vasodilation and histamine release compared to morphine and has minimal effects on the cardiovascular system. This agent is extensively utilized during geriatric anesthesia. However, in the elderly, clearance of fentanyl is decreased and terminal elimination half-life greatly prolonged.

Bentley et al (12) found almost a fourfold increase in elimination half-life of fentanyl in patients aged over 60 years compared to those aged under 50. Volumes of the central compartment and drug distribution were similar in all patients, but probably owing to reduced hepatic blood flow or reduced hepatic microsomal activity, clearance was markedly reduced.

Fentanyl has more prolonged effects in the elderly. The smaller dose requirements of this agent may not be related to pharmacokinetic factors alone. Variations in brain sensitivity due to changes at the opiate receptor with respect to receptor density and binding affinity may occur with aging. The preliminary results of a recent study of fentanyl and alfentanil dose requirements in the elderly suggest a pharmacokinetic explanation for changes in sensitivity to narcotics (13).

Volatile Agents

It has long been appreciated that the minimal alveolar concentration diminished with age (14). Of the volatile anesthetic agents in common use—halothane, ethrane, and isoflurane—the latter appears to cause the least disturbance of cardiovascular function.

Studies of the effects of the volatile agents in well-defined aged patient groups are limited, but it is likely that isoflurane produces the least change in cardiac output and blood pressure in the aged. When the merits of intravenous and inhalation agents for the elderly are being compared, the effects on regional blood flow are also important. In this respect there may be significant differences in regional blood flow responses to volatile agents in the aged.

Drug disposition changes in the aged (15). Most agents used as premedicants or induction agents or to maintain anesthesia have a greater effect and prolonged duration in the aged. Appropriate dosages are necessary to maintain hemodynamic stability during surgery and avoid cardiovascular and respiratory complications during the early postoperative period. Physiologic changes in the elderly, a reduction in lean body mass and body water, and an increase in body fat may produce marked changes in drug distribution when compared to the general adult population. It can be anticipated that drugs dependent on hepatic and renal function for elimination will have prolonged effects in the aged. As yet it appears, from the small number of studies performed, that changes in absorption, transport, binding, distribution, metabolism, and clearance are responsible for altered drug effects in the elderly. Whether pharmacokinetic changes alone are responsible remains controversial. The significance of pharmacodynamic factors in relation to the more profound response in the aged to agents used during anesthesia awaits further study.

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Nitroprusside Versus a Nitroprusside-Trimethaphan Mixture: A Comparison of Dosage Requirements and Hemodynamic Effects during Induced Hypotension for Neurosurgery

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Abstract

In this double-blind study the effects of sodium nitroprusside and a sodium nitroprusside-trimethaphan mixture were compared in 20 neurosurgical patients subjected to prior beta-adrenergic blockade. The dosage requirement of sodium nitroprusside to maintain hypotension was greatly reduced when the mixture was utilized. There were no major differences in standard hemodynamic variables or plasma renin activity.

Sodium nitroprusside (SNP), a potent, short-acting vasodilator, is frequently employed to induce hypotension during anesthesia. The major disadvantages of SNP are wide variability in individual response, tachyphylaxis, and cyanide toxicity. Trimethaphan (TMP) is a long-established hypotensive agent with both direct vasodilatory and ganglion-blocking actions. The relative merits of SNP and TMP are influenced not only by efficacy, but also by differing dose-related toxic effects and variations in effect on cerebral blood flow, cerebral metabolism, and the cardiovascular system.

In an attempt to obtain only the beneficial effects of SNP while reducing the risk of cyanide toxicity, SNP and TMP have been administered synchronously and also as a mixture (1–5). Clinical experience indicates that the total dose of SNP required is much reduced when these agents are used synchronously (1, 2). In patients undergoing otologic surgery a 1:10 mixture of SNP and TMP (SNP-TMP) produced easily controlled hypotension with marked reduction in the dosages of these drugs when compared to their use individually (3). The general circulatory effects of SNP-TMP appear similar or less profound than those of SNP (4). Blood cyanide levels are reduced following administration of SNP-TMP mixture, concomitant with the reduced SNP dose requirement, when compared with the use of SNP alone (5).

We have compared SNP and SNP-TMP mixture with respect to dosage requirements, hemodynamic changes, and variations in plasma renin activity (PRA) during anesthesia for neurosurgical procedures.

Patients, Material, and Methods

Twenty patients undergoing posterior fossa surgery in the sitting position for tumor removal participated in this study. All patients were aged 30–55 years, weighed 60–80 kg, and appeared free of cardiovascular, respiratory, or metabolic disease. Approval was obtained from our Institu-

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tional Research Advisory Committee, and informed consent was obtained from each patient.

Before surgery, patients were assigned randomly and equally to one of two groups. Hypotension was induced in group 1 with SNP and in group 2 with a 1:10 SNP-TMP mixture. Neither the anesthetist nor the investigator recording the data knew which hypotensive agent was being administered intraoperatively.

At noon on the day preceding surgery patients received propranolol, 40 mg, and dexamethasone, 4 mg by mouth; these doses were repeated three times at 6-hr intervals.

Premedication consisted of intramuscular secobarbital, 1.5 mg/kg 1 hr prior to induction of anesthesia. When the patient arrived in the operating suite, a peripheral infusion was begun, a 20-gauge catheter was placed in a radial artery, and a 7-French thermodilution pulmonary arterial catheter was introduced percutaneously from the antecubital fossa. Radial arterial, pulmonary arterial, and central venous pressures, as well as electrocardiogram leads II and V_5 were continuously monitored (Hewlett Packard 78901A). The arterial pressure transducer was maintained at the level of the head. Cardiac output (CO) was measured by a thermodilution technique in triplicate (Hewlett Packard 78231 C). The magnitude of neuromuscular blockade was assessed by train-of-four stimulation of the ulnar nerve. Esophageal temperature, urine output, end expired carbon dioxide levels, and precordial Doppler sounds (to detect air embolus) were also monitored throughout the procedure. Arterial blood gas analysis was intermittently performed, and mixed venous blood samples from the pulmonary artery were obtained for estimation of plasma renin activity as determined by radioimmunoassay (Clinical Assay Kit—Travenol Diagnostics).

Induction of anesthesia was achieved with thiamylal sodium, 6 mg/kg intravenously. Endotracheal intubation was facilitated with lidocaine hydrochloride, 1.5 mg/kg, and intravenous pancuronium bromide, 0.1 mg/kg. Anesthesia was then maintained with nitrous oxide (70%) and oxygen (30%). Controlled mechanical ventilation was instituted to maintain arterial carbon dioxide tension in a range of 25–30 mm Hg throughout surgery. Prior to application of skull clamps, fentanyl, 3 μg/kg, and lidocaine, 1.5 mg/kg, were administered intravenously. Further increments of fentanyl, 1.5 μg/kg, and pancuronium, 0.03 mg/kg, were administered intravenously before the skin incision, and, thereafter, anesthesia and muscle relaxation were maintained with continuous infusions of fentanyl, 1 μg/kg/hr, and pancuronium, 0.03 μg/kg/hr.

In both groups, hypotensive drugs were dissolved in 500 ml of 5% dextrose in water (group 1: SNP, 50 mg; group 2: SNP, 50 mg, plus TMP, 500 mg) and given by infusion pump. These solutions were protected from photodegradation and, when necessary, discarded 4 hr after preparation and replaced. Hypotension was induced after the skull was opened and the dura incised, and a mean blood pressure of 60–70 mm Hg was maintained throughout the period of intracranial manipulation until dural closure.

Hemodynamic measurements and blood samples were obtained: (a) prior to induction of anesthesia; (b) 30 min after the patient was positioned; (c) 1 hr after hypotension was induced; and (d) subsequently at hourly intervals throughout hypotensive anesthesia. On completion of surgery, lidocaine, 1 mg/kg, was given intravenously before head manipulation and residual paresis was reversed with neostigmine and atropine. Extubation was performed, and all patients were awakened in the operating room.

During transfer to the intensive-care unit, oxygen was administered by face mask and the electrocardiogram and mean arterial blood pressure were constantly monitored. Inappropriate hypertension during skull closure, transfer, or the immediate postoperative period was treated with vasodilator therapy as necessary.

Statistical significance for differences within the groups was evaluated by one-way, repeated-measures analysis of variance (ANOVA). Changes from baseline (awake) between the groups were assessed by unpaired Student's t test. The null hypothesis was rejected when $p < 0.05$. All data are expressed as mean ± SEM.

Results

The groups were similar with respect to age, weight, sex, mean duration of induced hypotension, and mean duration of anesthesia (Table 1). The total dose range of SNP was 2–40 mg (mean 18.9 ± 4.3) in group 1 and 0.7–10 mg (mean 3.6 ± 1.2) in group 2 ($p < 0.01$). The hourly dose range of SNP administered was 10–100 μg/kg (mean 49.5 ± 9.5) in group 1 and 2–36 μg/kg (mean 12.3 ± 3.6) in group 2 ($p < 0.01$). The highest total dose of SNP and TMP used in a group 2 patient was 10 mg SNP and 100 mg TMP.

Hemodynamic and hormonal data (Table 2) included a mean arterial pressure significantly lower during administration of the hypotensive

TABLE 1
Procedure Summary
(Mean ± SEM)

	Group 1 (SNP)	Group 2 (SNP–TMP)
Age (yr)	48 ± 3.9	43.2 ± 2.6
Weight (kg)	75.6 ± 4.5	69.8 ± 3.8
Sex (male:female)	6:4	4:6
Mean duration hypotension (min)	305 ± 43	274 ± 20
Mean duration anesthesia (min)	451 ± 41	448 ± 25
Mean total dose SNP (mg)	18.9 ± 4.3	3.6 ± 1.2*
Mean dose SNP (μg/kg/hr)	49.5 ± 9.5	12.3 ± 3.6*

SNP, sodium nitroprusside; TMP, trimethaphan.
* $p < 0.01$ compared to group 1.

solutions within both groups compared to baseline values. Cardiac output in group 2 was significantly reduced ($p < 0.05$) after 2 and 4 hr of induced hypotension compared to baseline values, whereas group 1 had no significant changes in cardiac output. There were no other significant differences within either group, nor were statistically significant differences found between the two groups in any of the hemodynamic variables measured.

Mean PRA levels were low and not significantly different in the two groups throughout the study. Overall PRA activity ranged from 0.4 to 5.0 ng/ml/hr during surgery in group 1 and from 0.3 to 12.6 ng/ml/hr in group 2. In group 2, PRA did not exceed 2.5 ng/ml/hr in 8 of 10 patients. However, in 2 patients, with glomus tumors, awake levels were 10.4 and 5.1 ng/ml/hr and 5.9 and 12.6 ng/ml/hr, respectively, following induction of anesthesia and positioning.

Discussion

Sodium nitroprusside therapy is associated with increased blood cyanide levels and the hazard of cyanide toxicity, which necessitates placing limitations on infusion rate and total dosage. Such restrictions may compromise the usefulness of this drug in procedures with large dose requirements. Pharmacologic regimens aimed at reducing SNP requirements may be directed at mechanisms that either inhibit reflex homeostatic responses to hypotension or directly potentiate the hypotensive effect of SNP. Examples of the former include preoperative propranolol (6–8) or captopril therapy (9). In this study, propranolol was utilized to achieve some degree of beta-adrenoreceptor blockade in all patients, and TMP was added to potentiate SNP in group 2 patients. The results indicate that the required dose of SNP is reduced four- to fivefold when it is administered as a 1:10 SNP-TMP mixture.

TABLE 2
Hemodynamic and Hormonal Data
(Mean ± SEM)

	Group	Awake	After positioning	Hours of hypotension			
				1	2	3	4
MAP (mm Hg)	1	91 ± 5	80 ± 5	70 ± 3†	69 ± 2†	69 ± 2†	73 ± 3*
	2	81 ± 5	72 ± 6	63 ± 2†	66 ± 3*	63 ± 2*	67 ± 5*
HR (beats · min^{-1})	1	72 ± 3	74 ± 3	73 ± 4	74 ± 3	73 ± 3	73 ± 3
	2	80 ± 3	82 ± 3	86 ± 4	89 ± 5	87 ± 5	89 ± 6
CVP (mm Hg)	1	5.7 ± 0.6	6.8 ± 1.1	6.0 ± 1.0	6.0 ± 1.4	7.6 ± 1.0	7.7 ± 1.2
	2	7.4 ± 0.9	5.9 ± 1.0	6.7 ± 1.3	6.2 ± 1.5	6.4 ± 1.0	7.2 ± 0.9
CO (L · min^{-1})	1	6.0 ± 0.4	5.8 ± 0.7	5.5 ± 0.8	5.0 ± 0.7	5.0 ± 0.7	6.3 ± 1.1
	2	6.1 ± 0.4	5.2 ± 0.3	5.3 ± 0.5	4.3 ± 0.4*	4.6 ± 0.4	4.2 ± 0.3*
PCWP (mm Hg)	1	6.2 ± 1.2	7.3 ± 1.5	6.6 ± 1.3	6.8 ± 1.7	5.7 ± 1.1	7.3 ± 1.4
	2	7.5 ± 1.2	7.6 ± 1.5	6.6 ± 1.4	6.9 ± 1.5	6.9 ± 1.7	6.7 ± 1.5
MPAP (mm Hg)	1	13 ± 2	13 ± 2	12 ± 1	11 ± 2	12 ± 2	12 ± 1
	2	11 ± 2	11 ± 2	12 ± 2	11 ± 2	11 ± 2	11 ± 2
SVR (dyn · sec · cm^{-5})	1	1222 ± 145	1090 ± 91	1110 ± 159	1147 ± 136	1138 ± 142	998 ± 161
	2	1170 ± 104	1107 ± 195	927 ± 92	1188 ± 134	1055 ± 106	1226 ± 175
PRA (ng/ml/hr)	1	1.36 ± 0.39	1.70 ± 0.46	1.12 ± 0.15	0.85 ± 0.19	1.38 ± 0.46	1.46 ± 0.59
	2	2.93 ± 0.87	2.76 ± 1.14	1.48 ± 0.28	1.70 ± 0.57	2.14 ± 0.93	2.26 ± 1.27
			N group 1:2	10:10	10:9	9:8	7:7

* $p < 0.05$ compared to awake.
† $p < 0.01$ compared to awake.
1 = (SNP); 2 = (SNP–TMP).

MAP, Mean arterial pressure; HR, heart rate; CVP, central venous pressure; CO, cardiac output; PCWP, pulmonary capillary wedge pressure; MPAP, mean pulmonary arterial pressure; SVR, systemic vascular resistance; PRA, plasma renin activity.

All patients received propranolol preoperatively, and as expected, mean PRA was low in both groups. Propranolol prevents reflex tachycardia during SNP-induced hypotension and inhibits or limits activation of the renin-angiotensin system (6, 7). The latter effect is considered to prevent the development of rebound hypertension on cessation of vasodilator therapy (8). Other species-dependent vasoactive substances may also be involved in the development of rebound hypertension; Zubrow et al (10) found that vasopressin plays an important role in the ewe, where falls in blood pressure of 10–20 mm Hg provoke a doubling of PRA but a 50-fold increase in vasopressin levels. We did not study this phenomenon, but rebound hypertension occurred in all 20 patients, necessitating ongoing vasodilator therapy during closure and the early postoperative period. It is possible that this response was, at least in part, related to inadequate levels of anesthesia, but we have previously often encountered rebound hypertension with other anesthetic techniques utilizing the routine propranolol dosage described. However, Fahmy (5), studying non-beta-adrenergic-blocked orthopedic patients, found rebound hypertension following administration of SNP but not the SNP-TMP mixture.

A reduction in dosage requirement of SNP and the severity of rebound hemodynamic effects following the use of SNP-TMP mixture may be anticipated. Augmentation of the effects of SNP by ganglionic blockade with tetrathylammonium or hexamethonium has been demonstrated in dogs (11). In humans, both SNP and TMP reduce blood pressure, but only the former is associated with elevated levels of plasma norepinephrine and epinephrine or with activation of the renin-angiotensin system (12). Induced hypotension with TMP does not provoke catecholamine release and inhibits renin release (12). Such differing effects suggest the possibility of a dual mechanism for SNP potentiation by TMP: supplemental vasodilation together with inhibition of renin release by ganglionic blockade. However, in our propranolol-pretreated patients, potentiation was not related to variations in PRA. Mean PRA levels in group 2 (SNP-TMP) were low, but numerically greater than in group 1 (SNP). This was a reflection of higher PRA preoperatively and during surgery in two patients in group 2 who underwent excision of the intracranial portion of glomus tumors. Glomus tumors may be capable of secreting catecholamines and activating the renin-angiotensin system (13). Nevertheless, in both patients hypotension was easily induced with low doses of SNP-TMP mixture.

The literature concerning SNP-TMP combinations is limited. Macrae et al (3) used a 1:10 SNP-TMP mixture for induced hypotension in 30 patients undergoing otologic procedures. They found a dramatic dose reduction with the mixture compared to their previous experience with SNP alone, despite often associated tachycardia. They considered the combination to be synergistic.

The same group of investigators studied the hemodynamic effects of a SNP-TMP mixture in 12 patients during anesthesia (4). Cardiac output did not change in 6 patients breathing spontaneously, but decreased significantly in 6 patients artificially ventilated whereas HR increased, and SVR and CVP decreased in all 12 patients.

Fahmy (5) found a threefold reduction in SNP requirement with a SNP-TMP mixture used to reduce mean arterial pressure to 55 mm Hg and also demonstrated much-reduced whole-blood cyanide levels following the use of the mixture. In his study, SNP reduced SVR and CO increased owing to increases in HR, whereas SNP-TMP reduced SVR without significant changes in CO or HR. Consequently, the effects of SNP-TMP may be particularly advantageous with respect to myocardial oxygen demand. In the present study, the hemodynamic effects of SNP and SNP-TMP in neurosurgical patients receiving propranolol were similar. There were no significant differences between the groups, and CO was well maintained throughout anesthesia. Changes in mean CO relative to reduction in MAP were not of sufficient magnitude to produce decreases in calculated SVR. Our failure to demonstrate differing hemodynamic effects of SNP and SNP-TMP mixture is probably due to the relatively small reduction in MAP required after patient positioning. In addition, the level of blood pressure maintained was higher than in the patients studied by Fahmy. Nevertheless, the reduction in SNP dose requirement in the patients receiving SNP-TMP mixture was significant.

To date, all reports concerning the SNP-TMP mixture consider only a 1:10 ratio of these agents. Such proportions have been chosen because they crudely represent the relative potency of the two drugs when used separately, and also in part for ease of preparation and administration. The chemical stability of the 1:10 mixture in 5% dextrose does not change over 4 hr (3). However, other ratios may prove to be even more efficacious.

In summary, the dose of SNP required to induce hypotension during neurosurgery was markedly reduced by the use of a 1:10 SNP-TMP mixture, and the hemodynamic effects of the mixture were similar to those of SNP alone. The mixture may be advantageous with regard to reducing the hazard of SNP toxicity during prolonged neurosurgical procedures.

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Anesthetic Problems in Joint Replacement Surgery

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Joint replacement surgery, one of the most consistently successful procedures in current orthopedic surgical practice, occupies a prime position in contemporary efforts to provide relief to patients disabled by severe joint pain and loss of function. Approximately 100,000 total hip replacements and 80,000 total knee replacements are performed each year in the United States, with excellent long-term results in most cases.

The majority of patients undergoing joint replacement surgery have degenerative joint disease, primarily osteoarthritic. Other diseases and conditions affecting the joints that are amenable to joint replacement are rheumatoid arthritis, failed operative repair of fractured hips, aseptic necrosis of the femoral head, metastatic lesions and pathologic fractures of the femur, Gaucher's disease, and traumatic fractures in the elderly patient. The management and etiology of the adverse cardiovascular response to polymethyl methacrylate bone cement is the most important anesthetic problem in joint replacement surgery. In addition, utilization of a deliberate hypotensive technique and choice of regional anesthesia are of some concern.

Bone Cement. The use of polymethyl methacrylate bone cement in joint replacement surgery is now well established. Of the adverse effects of polymethyl methacrylate bone cement, the most important of concern to the anesthesiologist are transient hypotension and cardiac arrest. Myocardial infarction, pulmonary embolus, cerebrovascular accident, and sudden death are sequelae of hypotension and cardiac arrest. Transient hypotension and cardiac arrest are serious adverse effects, and several cases with fatal outcome have been reported (1, 2). Thrombophlebitis and hemorrhage and hematoma may also occur.

Hypotension. Implantation of bone cement into the femoral shaft is frequently, but not invariably, followed by a transient hypotensive episode, and occasionally the fall in blood pressure is severe and catastrophic. The incidence of hypotension varies widely in different studies (1–6), which is not surprising given that the hypotensive episode may be brief and transient and that its detection is then dependent on the method of monitoring the blood pressure. The onset of hypotension can be rapid—within 1–3 min after cement instillation (1, 2). Some reports indicate that hypotension is more common when the initial systolic blood pressure is above 140 mm Hg and total fluid replacement including blood has been less than adequate (3). Elderly arteriosclerotic patients who compensate poorly for sudden changes in cardiovascular hemodynamics are particularly at risk (6). Because of the rapidity of onset, transience and variable severity of the hypotensive episode, early recognition is clearly important. Intraarterial cannulation and continuous direct monitoring of blood pressure is an accepted practice. This method of monitoring the blood pressure is mandatory in the high-risk group of patients referred to earlier. In addition, significant decreases in arterial oxygen saturation have been demonstrated shortly after insertion of polymethyl methacrylate bone cement. Intermittent sampling of arterial blood gases via an indwelling A line allows early recognition of desaturation and permits its correction by manipulation of respiratory and hemodynamic parameters.

More recently, continous monitoring of arterial oxygen saturation with pulse oximetry has become readily available in the operating room.

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Utilizing this simple, noninvasive method, significant changes in arterial oxygen saturation were seen during cement implantation in total knee replacement surgery (4).

Etiology of Adverse Cardiovascular Response. Although tissue toxicity of polymethyl methacrylate bone cement is not high, it has been suggested that the liquid polymethyl methacrylate monomer or its additives act as potent vasodilators when absorbed into the systemic circulation (2, 3). The forceful packing of cement into the femoral shaft and subsequent insertion and seating of the prosthetic device may result in very high intramedullary pressures. This, in turn, may force air, fat, and marrow contents, including liquid monomer, into the circulation, with consequent embolization to the lungs (7, 8). Alexander and Barron conducted a prospective study of 227 patients undergoing total hip replacement, and their investigation revealed clinical and biochemical evidence of disturbances consistent with pulmonary microembolism following insertion of cement and prosthesis into the femoral shaft in a large number of cases (9). Hypotension, relative hypoxemia, and lowered triglyceride and raised lipase levels characteristic of the pulmonary embolic syndrome were seen. In their study there was a significant fall in Pa_{O_2} after insertion of cement and prosthesis intraoperatively, which extended into the postoperative period. Kallos also demonstrated large decreases in arterial oxygen tension shortly after insertion of bone cement and prosthesis into the femur (8).

The marrow cavity is essentially a low-pressure chamber equipped with thin-walled blood vessels. Intramedullary pressures of several hundred torr have been demonstrated after insertion of prosthesis, and it is suggested that it is the rise in pressure that is important, not the nature of the inserted substance. It is postulated that even with effective venting drill holes in the femoral shaft and use of catheters, pressures are still high enough to cause intravasation of marrow contents, leading to pulmonary microembolization. There is considerable clinical evidence that embolism with fat globules, platelets, and fibrin aggregates occurs. Others have detected turbulence in the right side of the heart with esophageal stethoscopes and ultrasonic Dopplers after insertion of cement and prosthesis into the femur (10, 11).

The emboli are carried from the right heart into the small arterioles and capillaries of the pulmonary circulation, where they cause blockage and become coated with platelets. These microemboli are then hydrolyzed by lipase into free fatty acids which are toxic to the lung parenchyma, causing disruption of alveolar-capillary membranes and resulting in hemorrhages and alveolar collapse. In addition, mechanical blockage of capillaries leads to diffusion block and increased arteriovenous shunting. The aggregation of platelets is also responsible for the release of vasoactive substances such as serotonin and histamine, which may also be a causal factor in the hypotension seen with pulmonary embolic syndrome. Furthermore, a sudden increase in pulmonary vascular resistance with transient reduction of return to the left side of the heart may be a contributing factor. Measurement of arterial oxygen tension or continuous oxygen saturation has been stressed as the most important monitoring parameters during the period after insertion of cement and prosthesis (9).

More recently, Roewer and colleagues reported on the use of two-dimensional transesophageal echocardiography to detect embolic events in the right heart during hip surgery (10). They studied 12 elderly patients undergoing total hip replacement for repair of transcervical fractures of the femoral neck and observed a transient increase in contrast intensity in the right atrium after application of cement and acetabular component, which was even more pronounced after insertion of cement and prosthesis into the femoral shaft. In addition, in 10 of the 12 patients they noted significant reduction in arterial oxygen tension after the appearance of contrast in the right atrium.

Air embolism has also been shown to occur during total hip replacement surgery. Michel studied 49 patients undergoing hip surgery and detected the sounds of air emboli by auscultation in 30% (11). Anderson also reported the ability to detect small amounts of air in 5 of 6 patients (12).

Deliberate Hypotensive Anesthesia. Joint replacement surgery is associated with substantial blood loss. A deliberate hypotensive anesthetic technique in appropriately selected patients undergoing hip replacement has been shown to reduce intraoperative blood loss and the need for blood transfusion and thereby reduce the risks associated with the transfusion of banked blood (13–16). Another advantage of decreased blood loss is the provision of better surgical conditions and the improved bonding of polymethyl methacrylate bone cement to bone (14, 15).

Thompson and her colleagues studied a group of elderly patients with fractured hips scheduled for total hip replacement under a deliberate hypotensive technique. These researchers evaluated cerebral, renal, and hepatic function and showed that deliberate hypotension to a mean arterial pressure of 50 torr during total hip arthroplasty decreased operating time, blood loss, and the number of transfusions needed without apparent injury to heart, brain, liver, or kidney (15). Although several authors have advocated controlled hypotensive anesthesia for total hip replacement surgery, the experience of others is that the poor physical status of many elderly patients requiring hip arthroplasty precludes the use of a significant degree of hypotension and hence may persuade some to adopt a more cautious approach to deliberate hypotensive anesthetic techniques in the elderly (17).

Regional Versus General Anesthesia. Keith studied three groups of patients undergoing total hip replacement with epidural anesthesia, general anesthesia with halothane, and a modified neuroleptanesthetic technique, comparing intraoperative blood loss (14). He demonstrated a significant decrease in intraoperative blood loss and the need for transfusion in the epidural group. In his study there was no significant difference in the degree of fall in arterial blood pressure in the three groups, and he postulated that in addition to the decrease in cardiac output, there is a decrease in the regional blood flow at the operative site to account for the decreased blood loss in the epidural group. This effect is probably due to a redistribution of circulating blood volume to the dependent hip caused by a reduction of venous pressure as a consequence of the lateral position of the patient and also by a decrease in sympathetic tone (13–14).

Blood Loss. Rosberg et al compared blood loss in total hip replacement with four different anesthetic techniques (13). They demonstrated substantial reduction in intraoperative bleeding in the group undergoing deliberate hypotension with sodium nitroprusside and commented that the reduced bleeding facilitated the surgeon's work. Epidural anesthesia also reduced blood loss as compared to the "normotensive" technique.

Spinal and Epidural Anesthesia. Another explanation offered for the reduced bleeding in the epidural group may be that the controlled ventilation often used with general anesthesia may increase intrathoracic and venous pressures. The absence of this mode of ventilation in the epidural group may be another reason for the decreased blood loss (18).

In the Rosberg study 0.5% bupivacaine was used for epidural blockade. An added benefit of the technique was that patients commonly remained pain-free for several hours postoperatively when compared to those given general anesthesia. A further advantage of the regional technique for total hip replacement is that substantial pain relief is made possible by administration of epidural narcotic analgesics. Modig et al compared parenteral analgesics and continuous extradural block regimens postoperatively in patients subjected to total hip replacement surgery and demonstrated that postoperative arterial oxygenation was better in the epidural group (19).

In addition to the above considerations, regional anesthetic techniques—spinal and epidural anesthesia—for joint replacement surgery have also been reported to offer the distinct advantages of reduced blood loss in the operative field, with consequent reduction in the need for intraoperative blood replacement and significantly decreased time of surgery (13–15). Rosberg et al, in a prospective study, evaluated blood loss during total hip arthroplasty and the relation of four different anesthetic techniques (13). They concluded that blood loss was significantly reduced in the sodium nitroprusside-induced hypotensive group as well as the epidural group when compared with the general anesthesia groups using halothane or neuroleptanesthesia. The authors considered controlled hypotension a useful adjuvant in anesthesia for total hip replacement in selected patients and epidural anesthesia a suitable anesthetic technique for most patients.

Thorburn et al studied 85 patients undergoing total hip replacement and assessed the frequency of deep vein thrombosis and total intraoperative blood loss (20). They reported a reduction of blood loss in the spinal anesthesia group of 66% compared with the general anesthesia group, and a total blood transfusion volume of 52% in the spinal anesthesia group compared with the general anesthesia group. In addition, they reported a significant reduction in the frequency of deep vein thrombosis, assessed by fibrinogen uptake studies and venography in patients receiving spinal anesthesia (20). Their conclusion was that spinal anesthesia offers considerable advantages over general anesthesia by decreasing the frequency of deep vein thrombosis, blood loss, and requirements for blood transfusion during total hip replacement. Deep vein thrombosis is a relatively common complication following major orthopedic surgery involving the hips, such as total hip replacement and other procedures to repair fractures. An incidence of 20%–30% has been reported following total hip replacement. Prophylactic measures such as miniheparin therapy and the use of low-molecular weight dextran have generally been disappointing. Modig et al studied 30 patients undergoing total hip replacement and compared the influence of extradural anesthesia with general anesthesia on fibrinolysis inhibition and fibrinogen activity (17). Their analysis revealed better fibrinolytic activity in patients given extradural anesthesia than in those who received general anesthesia. They commented that this observation confirmed their previous experience that the incidence of deep vein thrombosis and pulmonary embolism was lower with the use of extradural anesthesia.

Management of Anesthesia for Joint Replacement Surgery

Thus the major problems in management of anesthesia for joint replacement surgery are (a) adverse cardiovascular response to polymethyl methacrylate bone cement: arterial desaturation with severe hypotension and cardiac arrest, and (b) significant intraoperative blood loss. Clearly, it is essential to detect decreases in arterial oxygen saturation as early as possible and institute corrective therapy by manipulating inspired oxygen concentration and ventilatory parameters. Meticulous attention to adequate intraoperative fluid management and replacement of significant blood loss is required to prevent severe hypotension. A deliberate hypotensive technique in the appropriately chosen patient has been shown to attenuate the adverse cardiovascular response to polymethyl methacrylate bone cement. If hypotension occurs in spite of these measures, aggressive vasopressor therapy may be required.

A deliberate hypotensive technique in joint replacement surgery offers the advantage of reduced blood loss and in addition provides improved surgical conditions and bonding of cement and prosthesis. In the properly chosen patient, spinal and epidural anesthesia has considerable advantages over general anesthesia in joint replacement surgery. Reduced blood loss and decreased incidence of postoperative deep venous thrombosis are clearly advantageous. In addition, a continuous epidural technique will facilitate management of postoperative pain with use of epidural narcotics. In addition to these advantages, postoperative confusion and disorientation are less common in the older patient with spinal/epidural anesthesia than with general anesthesia. This is of considerable importance in the nursing care and management of the elderly in the immediate postoperative period.

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Cardiac Dysfunction in Alcoholics

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Abstract

To assess one possible reason for the high mortality rate in alcoholics, 50 consecutive alcoholics were studied prospectively with noninvasive tests during detoxification in a hospital. On admission, none were known to have cardiac disease; 34 (of the 50) had blood pressures greater than 140/90; none had significant cardiovascular findings. Twenty-four hour Holter monitoring disclosed tachyarrhythmias in 48, bradyarrhythmias in 4, and ventricular tachycardia in 4. Neither drinking history, resting electrocardiogram, nor routine laboratory parameters were predictive of arrhythmia potential. In 3 of the 4 with ventricular tachycardia, the arrhythmias were no longer observed on follow-up Holter monitoring 1 week after admission.

Of 20 patients followed up at 2 years, 4 had died, 6 were totally abstinent, and 10 had resumed drinking. All had sinus tachycardia on Holter monitoring. PEP/LVET ratio was higher in actively drinking alcoholics than in abstinent alcoholics. Left ventricular ejection fraction was greater than 50% in all.

Thus, although arrhythmias frequently complicate alcohol withdrawal, they are usually self-limited. Continuation of alcohol abuse is associated with increased PEP/LVET. In addition, mortality is at least 8% within 2 years of admission for alcohol detoxification.

A wide spectrum of cardiac abnormalities following both acute and chronic ingestion of alcoholic beverages has been reported in alcoholics (1–14). Although increased mortality has been reported in male alcoholics (15), little is known about conduction abnormalities, arrhythmias, and sudden death following abrupt stopping of alcohol intake (16, 17). The purpose of this prospective study was to evaluate rhythm disturbances and myocardial function by noninvasive techniques in male alcoholics admitted for detoxification and to correlate such changes with physical examination and biochemical tests.

Patients, Materials, and Methods

Initial Study. Fifty consecutive male alcoholics who had consumed alcohol ($\bar{x} = 223 \pm 18$ gm/day $\times$ 24 $\pm$ 2 yr) until admission to the Bronx VA Medical Center for alcohol detoxification were evaluated. Subjects ranged in age from 24 to 66 years (mean 44 ± 2). No patient had a history of cardiac disease, nor did any have physical complaints referable to the cardiovascular system. None had signs of alcohol withdrawal syndrome at the time of admission.

On admission, all patients underwent a complete history-taking and physical examination. Blood was obtained for complete blood count, prothrombin time, and chemistry profile (SMA-18). In addition, breath alcohol analysis and chest x ray were obtained.

After admission, patients were treated with general supportive measures, minor tranquilizers, if needed, for manifestations of the alcohol withdrawal syndrome, and vitamin supplements, if deemed necessary by nutrition consultation.

Cardiac Evaluation. A 12-lead scalar electrocardiogram was obtained on admission. Twenty-four-hour Holter monitoring was performed within 24 hr of admission and cessation of alcohol in all subjects. Repeat Holter monitoring was

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performed within 1 week in all four subjects who manifested ventricular arrhythmias on the initial Holter monitor. All tapes were adequate for interpretation and were interpreted by a single investigator without knowledge of the clinical or laboratory parameters. One tape was only 12 hr in duration. The tapes were scanned on a Del Mar Avionics Trendsetter arrhythmias analyzer model 9020 with a DCG graphics printer for making hard copy of the arrhythmias.

Echocardiographic Measurements. Echocardiograms were obtained in all patients within 24 hr of admission and were of good quality in 44 subjects. An IREX 101 ultrasound unit with a probe diameter of 1.27 cm and 2.25 MHz transducer focused on 10 cm with a repetition rate of 1000 impulses/sec was employed for these tracings. Echocardiograms were recorded with the subjects in a slight left lateral decubitus positiion. Aortic root and left atrial dimensions were recorded by angling the ultrasonic beam for the mitral valve into the aortic root. Measurements were made according to recommendations of the American Society of Echocardiography (18). The ventricular dimensions were measured at the level of the cordae tendinae. All diastolic measurements were made at the beginning of the QRS complex, as recommended by the Committee on M-mode Standardization of the American Society of Echocardiography (18).

The following left ventricular dimensions were obtained: (a) end-diastolic diameter (Dd) measured in millimeters at the time of "R" wave peak; (b) end-systolic diameter (Ds) measured in millimeters at the shortest internal diameter during the same cardiac cycle; (c) end-diastolic (EDV) and end-systolic (ESV) volumes calculated in millimeters by using the cubes of the diameter; (d) stroke volume (SV) measured in millimeters and calculated as end-diastolic ventricular volume minus the end-systolic ventricular volume; (e) ejection fraction (EF) expressed as a percentage and calculated as the ratio of stroke volume/end-diastolic volume; (f) percentage of change in minor-axis diameter (%D) calculated as end-diastolic diameter minus end-systolic diameter over end-diastolic diameter times 100.

The following formulae were used (19, 20):

(1) Ejection fraction (EF)

$$\frac{\text{EDV} - \text{ESV},}{\text{EDV}}$$

where EDV = end-diastolic volume, ESV = end-systolic volume, and SV = stroke volume. Cardiac volumes were calculated according to Teichholz correction.

(2)

$$V = D^3 \times \frac{7.0}{D + 2.4}$$

where V = volume, D = dimension.

(3) Shortening fraction (SF%)

$$\frac{\text{Dd} - \text{Ds}}{\text{Dd}} \times 100$$

where Dd = diastolic dimension, Ds = systolic dimension.

Systolic Time Intervals. Systolic time intervals (STI) were calculated from lead II of the electrocardiogram and the phonocardiogram at the left sternal border, and an external carotid pulse tracing was done simultaneously at a paper speed of 100 mm/sec. Five complexes were measured and averaged (all patients had sinus rhythm). The total electromechanical systole ($Q\text{-}S_2$) was measured from the beginning of the QRS complex to the first rapid deflection of the second heart sound. Left ventricular ejection time (LVET) was measured in msec from the upstroke of the carotid pulse to the nadir of the incisural notch. Preejection period (PEP), measured in msec, was calculated as the difference between the $Q\text{-}S_2$ interval and the LVET. All systolic time intervals were corrected for the heart rate using a normal regression equation, with the exception of the PEP/LVET ratio.

Gated Blood Pool Scintigraphy. Gated blood pool scans were performed at rest. Studies were performed with two general all-purpose collimators interfaced with an apex 415 dedicated minicomputer system for enough counts to achieve pixel saturation, usually a total of 6 million counts per study. Imaging was performed in the anterior, extreme left anterior oblique, and left anterior oblique projection providing the best septal separation. Processing of the image included temporal smoothing followed by a standard nine-point spatial smoothing. The region of interest was drawn using an irregular node; the determination of the left ventricular edge was performed automatically, using a combination of the second derivative function of the count rate profile and an absolute threshold level. The background was computer-assigned, three pixels from the left ventricular posteroinferior border (90°–180° arc), three pixels wide. The left ventricular ejection fraction (LVEF) was calculated from the time-activity curve where (after background subtraction) LVEF = (LV end diastolic counts − LV end systolic counts)/LV end diastolic counts.

Follow-up Evaluation. Two years after the initial evaluation, attempts were made to contact

TABLE 1
Correlation of Clinical and Laboratory Findings at Admission, 50 Asymptomatic Alcoholic Men Admitted for Detoxification (Mean ± SEM)

	Total	VT	SVT	ST	SB
Age (yrs)	44 ± 2	56 ± 2	57 ± 3	48 ± 2	35.5 ± 6
Alcohol intake	223 ± 18	123 ± 44	166 ± 54	206 ± 34	185 ± 65
(gm/day × yrs)	×24 ± 2	×35 ± 6	×33 ± 5	×27 ± 2	×20 ± 6
BP (mm Hg)					
Systolic	135 ± 3	142 ± 7	141 ± 8	134 ± 4	134 ± 9
Diastolic	87 ± 1	90 ± 6	92 ± 2	88 ± 2	84 ± 6
Alcohol (mg%)	81 ± 16	95 ± 60	90 ± 70	59 ± 25	61 ± 48
BUN (mg/dl)	9.8 ± .6	13 ± 3.6	8.8 ± 2	10.2 ± 1	11 ± 3.3
GLUC (mg/dl)	116 ± 9	118 ± 10	100 ± 8	134 ± 21	112 ± 12
CA (mg/dl)	10.0 ± 0.1	9.9 ± 0.2	9.9 ± 0.2	10.2 ± 0.1	9.9 ± 0.1
PHOS (mg/dl)	3.5 ± 0.1	3.3 ± 0.7	4.0 ± 0.2	3.2 ± 0.1	3.6 ± 0.3
K (mEq/L)	4.2 ± 0.1	3.8 ± 0.3	4.0 ± 0.1	4.3 ± 0.1	4.1 ± 0.2

Total, entire group; VT, ventricular tachycardia; SVT, supraventricular tachycardia; ST, sinus tachycardia; SB, sinus bradycardia.

these 50 subjects. Four were known to be deceased: 1 from liver disease, 1 from metastatic carcinoma, 1 most likely secondary to cardiac disease, and the fourth of unknown causes. Sixteen were reevaluated; of these, 6 had totally abstained from alcohol since the first evaluation. Of the remaining 10, alcohol histories were felt to be unreliable owing to underreporting in 7. The remaining 3 consumed 160 gm/day between the initial and follow-up studies.

At the time of follow-up, all subjects underwent a complete history-taking and physical examination. Blood was obtained for complete blood count, magnesium, and SMA-18 chemistry profile. All underwent breath alcohol analysis. Abstinent patients had a Holter monitor, echocardiogram, systolic time intervals, gated blood pool scan and an electrocardiogram performed as outpatients. Actively drinking patients were admitted for detoxification. On admission, electrocardiogram, systolic time intervals, echocardiogram, and Holter monitoring were done. All had a gated blood pool scan performed within 1 week of admission.

Results

Initial Study

Clinical Results. Thirty-four subjects had admission blood pressures equal to or greater than 140/90 at the time of admission. In the majority of patients, blood pressure returned toward normal with abstinence. Cardiac examination was normal on admission in 41 subjects, but in 6 an S_4 gallop was present, and in 3 flow murmurs were heard.

Laboratory Findings. Correlations of laboratory findings for the total group, as well as for the subgroups (Table 1), showed four (of 50) had serum potassium outside the normal range. In two there was no arrhythmia, whereas 1 patient manifested sinus tachycardia and the fourth had ventricular tachycardia. No other significant electrolyte abnormalities were apparent. Serum magnesium was not obtained in the majority of subjects, but it was decreased in a single individual with ventricular tachycardia. Blood alcohol levels were not helpful in predicting arrhythmogenic potential.

Electrocardiographic findings (Table 2) included nonspecific ST-T changes observed in the majority of subjects. Approximately 20% had manifestations of early repolarization. Premature atrial or ventricular contractions were rare, each being present in 2 (of 50) patients.

By contrast with the admission electrocardiogram, Holter monitoring (Table 3) disclosed an increased prevalence of arrhythmias in this group: sinus tachycardia in 48, atrial tachycardia in 4, ventricular tachycardia in 4, and sinus bradycardia in 4. Additionally, atrial premature contractions were observed in 46 and ventricular

TABLE 2
Admission Electrocardiographic Findings in 50 Asymptomatic Alcoholic Men Admitted for Detoxification

Abnormality	No. of subjects
Nonspecific ST-T changes	37
Early repolarization	9
Sinus tachycardia	4
Atrial premature contractions	2
Ventricular premature contractions	2
Left axis deviation (−30°)	2
Left anterior hemiblock (−45°)	5
Left ventricular hypertrophy	3

TABLE 3
Holter Monitor Findings in 50 Alcoholic Men Admitted for Detoxification

Abnormality	No. of subjects
Sinus tachycardia	48
Atrial tachycardia	4
Ventricular tachycardia	4*
Sinus bradycardia	4

Recordings within 24 hr of cessation of alcohol.

* Resolved in 3 on repeat testing after 1 week of hospitalization.

premature contractions in 28. Several patients manifested more than one abnormality. Thus, in the first 24 hr after cessation of alcohol intake, Holter monitoring yields a higher percentage of arrhythmias than would be expected from the baseline electrocardiogram. Of particular interest, 4 subjects manifested episodes of ventricular tachycardia (Figure 1). In 3 of these 4, the arrhythmias were not present on follow-up Holter monitoring 1 week later. In the single patient with persistent arrhythmias, both serum magnesium and potassium were decreased. Despite correction of both electrolyte abnormalities the arrhythmia persisted and was not suppressed when procainamide 6 gm/day was administered.

Gated blood pool scans were performed in the 4 patients with ventricular arrhythmias. The one subject with persistent arrhythmias had hypokinesis of both right and left ventricles and an ejection fraction of 22%.

Echocardiograms were interpreted as normal in 42 of the 50 patients. In 2, there was calcification and/or fibrosis of the aortic root, without aortic valve involvement; in 4, there was mild to moderate dilatation of the left ventricular cavity. In 1, a minimal posterior pericardial effusion was present, and in another, the echo was suggestive of mitral valve prolapse.

Systolic time intervals (Table 4) showed no difference between any of the groups in either PEP_c or $LVET_c$. However, the mean for all groups was at the upper normal limit (0.11) for the PEP_c. Likewise, for the $LVET_c$, although there was no marked difference between these groups, mean values for each group approached the upper normal limit (0.40). By contrast, all groups had normal ratios for the PEP/LVET.

Follow-up Study

Clinical Data. Blood pressures were <140/90 in all abstinent subjects. In 7 of the 10 actively drinking patients, the pressure was elevated. Cardiac examination was normal in 7. An S_4 gallop was present in 1, ectopy was observed in 1, and a flow murmur was heard in another patient. **Laboratory Data.** Again, as at the time of initial evaluation, laboratory findings did not correlate with arrhythmias. Serum magnesium was minimally decreased in 1 of the abstinent patients and in 4 of the actively drinking subjects.

Again, repeat electrocardiograms demonstrated nonspecific ST-T wave changes in a majority of subjects. By contrast with the electrocardiogram, Holter monitoring revealed intermittent sinus tachycardia in all subjects. Five of the 6 abstinent subjects had episodes of bradycardia whereas only 6 of the 10 drinking subjects had such episodes. Of the abstinent subjects, 1 patient had short runs of atrial tachycardia. All 6 abstinent subjects had rare atrial premature contractions; 5 had occasional ventricular premature beats. By contrast, 1 of the actively drinking subjects had ventricular tachycardia, which resolved spontaneously with abstinence. Likewise, all actively drinking subjects had atrial premature contractions, and 7 of these 10 had ventricular premature beats.

Echocardiograms were interpreted as normal

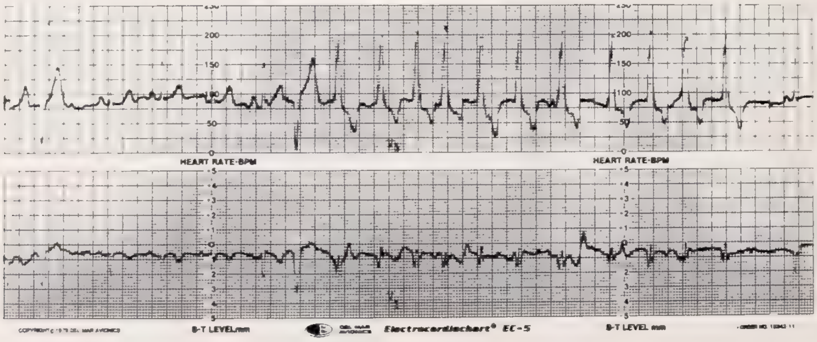

Fig. 1. Representative tracing of Holter monitor recording showing ventricular tachycardia in an asymptomatic alcoholic during the first 24 hr following abstinence from alcohol.

TABLE 4

Comparison of PEP_c, $LVET_c$, and Ratios of PEP/LVET in 50 Alcoholic Men Admitted for Detoxification and Manifesting Asymptomatic Arrhythmias

	Total	VT	SVT	ST	SB
PEP_c	0.12 ± 0.00	0.12 ± 0.01	0.14 ± 0.00	0.12 ± 0.01	0.11 ± 0.01
$LVET_c$	0.40 ± 0.00	0.41 ± 0.01	0.40 ± 0.02	0.39 ± 0.01	0.41 ± 0.01
PEP/LVET	0.35 ± 0.01	0.30 ± 0.04	0.33 ± 0.05	0.35 ± 0.02	0.30 ± 0.03

in 4 of the 6 abstinent alcoholics. The fifth had a mildly dilated left ventricle, and in the sixth there was a suggestion of mitral valve prolapse. By contrast, all drinking alcoholics had normal echocardiograms.

Systolic time intervals (Table 5) showed a mean value for PEP_c mildly increased (0.14) in both the abstinent and the actively drinking alcoholics. Likewise, although the mean values for the $LVET_c$ were comparable in the two groups, values tended to be slightly lower in the actively drinking subjects. At 2-year follow-up (Fig. 2), values for PEP/LVET were higher in the actively drinking group than in the abstinent subjects. The PEP/LVET increased during the 2-year interval in the majority of those who continued to consume alcohol.

Gated blood pool scans were performed in all abstinent alcoholics and 9 of the 10 actively drinking subjects. Left ventricular ejection fraction was greater than 50% in all subjects.

Discussion

The prognosis for alcoholics manifesting the withdrawal syndrome correlates with the severity of the withdrawal (21). A report by Thompson et al (22) cites a death rate of 7% for persons with full-blown delirium tremens. One factor that may be associated with an adverse prognosis is hypokalemia, especially in subjects receiving cardiac glycosides (23). Although 4 of our subjects did have low serum potassium levels, none was receiving cardiac medication. In 2 of these, no arrhythmia was noted on the initial Holter monitoring. The third subject manifested sinus tachycardia only. The fourth, however, had an associated magnesium deficiency as well as evidence of a severely hypokinetic myocardium. In this subject there was evidence of ventricular tachycardia on Holter monitoring, both on admission and during follow-up evaluations. It is possible that the etiology of this patient's arrhythmia was multifactorial.

Mehta and Sereny (24) noted an increased frequency of sinus tachycardia and ventricular premature beats in 70 alcoholics admitted for alcohol withdrawal. Their subjects were assessed 24–48 hr following cessation of drinking. Abbasakoor et al (16) studied electrocardiographic changes in 50 acutely intoxicated males with 12-hr Holter monitoring at the time of admission for treatment of alcoholism (satisfactory records were obtained in only 36 of the 50 subjects). These authors still noted a 3% incidence of ventricular tachycardia in their patients. In addition, 33% of their subjects had ventricular ectopy. Our findings are consistent with this report, in that 8% of our patients manifested ventricular tachycardia and 56% had ventricular ectopy on the 24-hr Holter monitor. Similarly, the incidence of hypokalemia was low in our series and did not correlate with ventricular ectopy.

More recently, Ballas et al (17) reported results of Holter monitoring in 50 consecutive subjects admitted in alcohol withdrawal. These authors were unable to improve diagnostic yield from daily baseline electrocardiograms. However, only 17 of their subjects had interpretable tracings. It is unclear how soon after admission the monitoring could be performed. These authors did record a considerable number of abnormalities on resting electrocardiograms.

Systolic time intervals were also performed in 24 of the 50 subjects studied by Ballas et al (17). Compared to their group of normals, they noted increased PEP, decreased LVET index, and increased PEP/LVET ratio in their group of alcoholics. Similarly, we have noted increased PEP. However, mean LVET was normal for the entire group and approached normal for each of the subgroups. By contrast with the patients of Ballas et

TABLE 5

Comparison of PEP_c, $LVET_c$, and PEP/LVET in 16 Alcoholic Men 2 Years following Alcohol Detoxification

	PEP_c	$LVET_c$	PEP/LVET
Total ($n = 16$)	0.14 ± 0.00	0.39 ± 0.00	0.44 ± 0.02
Abstinent ($n = 6$)	0.14 ± 0.00	0.40 ± 0.00	0.40 ± 0.04
Drinking ($n = 10$)	0.14 ± 0.00	0.38 ± 0.00	0.46 ± 0.02

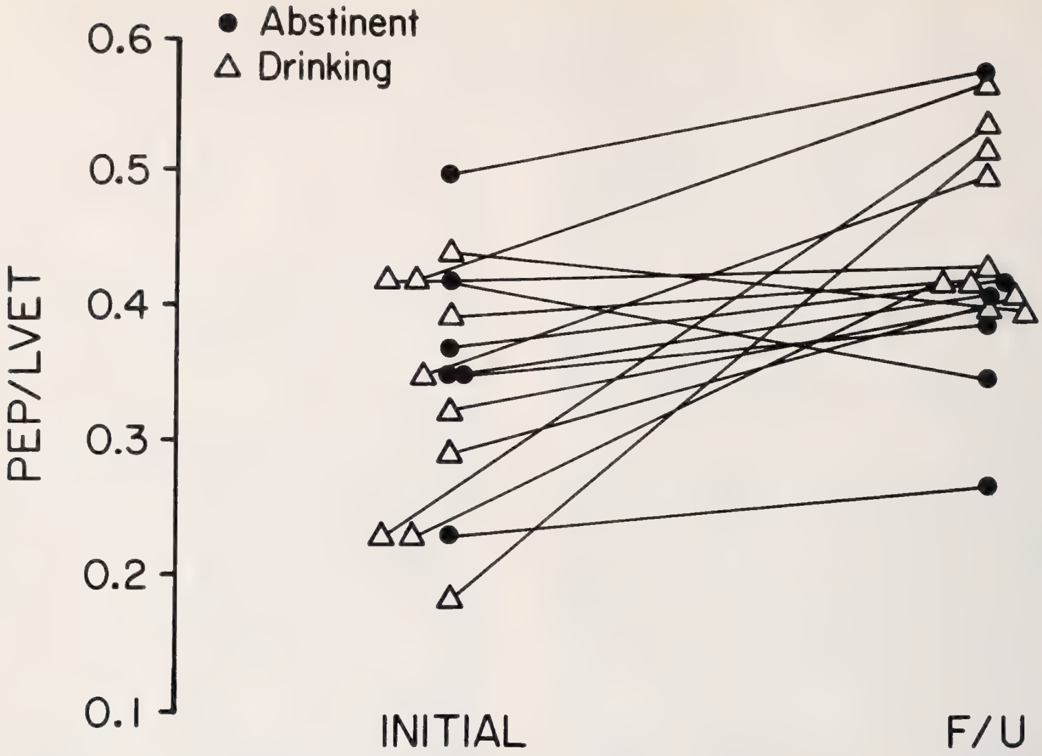

Fig. 2. Initial and 2-year follow-up of PEP/LVET in 10 actively drinking and 6 abstinent alcoholics. The PEP/LVET increased during the 2-year interval in the majority of the actively drinking patients.

al, our subjects demonstrated normal PEP/LVET ratios. Although values for PEP/LVET are greater than the control values reported by Ballas et al, they are more consistent with the control values reported by Gould et al (25), who found variable effects of an acute dose of alcohol on PEP and LVET, reflecting underlying cardiac disease. By contrast with our results, Schweitzer and Mark (26) reported increased PEP/LVET in a group of chronic alcoholics. However, all patients in that study had biopsy-proven liver disease, and the results may not be directly comparable to our current population. By contrast with the results observed on the initial evaluation, PEP at follow-up was mildly increased in all subjects. LVET was decreased in actively drinking alcoholics as compared to abstinent subjects, and PEP/LVET had increased more in the actively drinking as compared to the abstinent alcoholics. The results at the 2-year follow-up in the actively drinking patients thus confirm the data of Schweitzer and Mark. The differences seen on the initial studies may therefore reflect the earlier stage of cardiac dysfunction.

Left ventricular ejection fractions, as assessed by gated blood pool scans, were normal in all subjects. This is in contrast to the group evaluated by Read et al (27) in which 70% of subjects had values less than 50%. A positive blood alcohol level may, in part, account for the disparate results, since Kelbaek et al (28) have reported that the left ventricular ejection fraction may be decreased by 11% at rest in healthy subjects following an acute dose of alcohol.

In conclusion, a significant percentage of asymptomatic alcoholic patients manifest cardiac arrhythmias following abrupt cessation of alcohol. These arrhythmias are usually self-limited in the majority of subjects. Left ventricular dysfunction may, in part, account for the abnormalities observed. Continued consumption of alcohol is associated with increased PEP/LVET. In addition, there is, at a minimum, an 8% mortality at 2 years in "asymptomatic" alcoholics admitted for detoxification.

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The Relationship of Dyspnea on Exertion to Stress-Induced Thallium-201 Lung Uptake

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Abstract

Dyspnea is a symptom commonly associated with high pulmonary venous pressure that often occurs with severe myocardial dysfunction. Increased lung uptake of thallium 201 (TI-201) with exercise has been reported to occur with significant myocardial dysfunction. Dyspnea on exertion might, therefore, be expected to occur more frequently in patients with increased TI-201 lung uptake. We identified 25 patients with increased lung uptake of TI-201 and coronary artery disease (group 1), 16 patients with coronary artery disease and normal lung TI-201 uptake (group 2), and 18 patients without coronary artery disease or increased lung TI-201 uptake (group 3). Patient groups were compared for incidence of dyspnea on exertion by history and at the time of treadmill stress testing. Pulmonary function testing was not performed in this retrospective study.

The exercise double products and maximal exercise heart rate divided by maximal predicted heart rate were lower in group 1 than in group 2 ($p < 0.05$). The presence of increased myocardial dysfunction was suggested by a greater frequency of apical TI-201 defects in group 1 than in group 2 (9/25 vs 1/16, $p < 0.05$). A history of dyspnea was more frequent in group 1 patients than in group 2 (14/25 vs 4/16, $p \leqslant 0.05$) or in group 3 (4/18, $p < 0.05$). Dyspnea at the time of exercise testing, however, did not occur more frequently in any group (4/25 vs 2/16 vs 1/18). Interestingly, of patients in group 1 with a history of dyspnea on exertion, more had exercise-limiting fatigue than dyspnea (8/14 vs 3/14, $p \leqslant 0.05$).

We conclude that while exertional dyspnea by history correlates with increased lung uptake of TI-201, dyspnea at the time of exercise testing does not correlate with this previously described marker of exercise-induced myocardial dysfunction.

Myocardial perfusion imaging with thallium 201 (TI-201) has been used clinically for the evaluation of patients with suspected coronary artery disease since 1975 (1–7). More recently, attention has been focused on increased lung uptake of TI-201 after exercise as a manifestation of left ventricular dysfunction. The presence of increased TI-201 lung uptake has been shown in animal studies to correlate with higher left atrial pressures and abnormal pulmonary transit times (8). Clinical studies have revealed an association with higher pulmonary capillary wedge pressures in patients undergoing simultaneous cardiac catheterization and exercise TI-201 studies (9). In addition, more severe and extensive coronary artery disease as well as left ventricular dysfunction have been found in patients with exercise-induced increased lung TI-201 (8–12).

Dyspnea, which has been defined as "an abnormally uncomfortable awareness of breathing" (13), is a common symptom of patients with left ventricular dysfunction. It is commonly felt to be a clinical expression of pulmonary venous and capillary hypertension and congestion. Exertional dyspnea, if it is cardiac in origin, strongly

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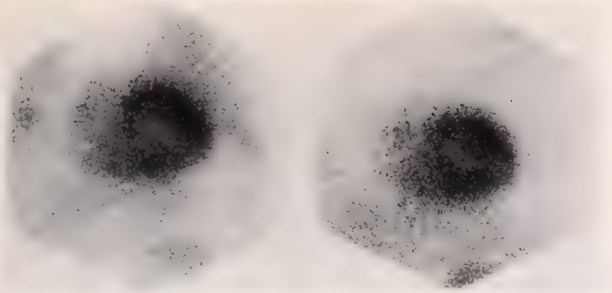


Fig. 1. Anterior views of thallium-201 scintigrams immediately after exercise (left) and three hours later in a patient with exercise-induced increased lung uptake.

suggests left ventricular failure, and should be expected to occur more frequently in patients with exercise-induced left ventricular dysfunction.

The present study compares the incidence of dyspnea on exertion (both by history and at the time of TI-201 stress testing) with the presence of exercise-induced increased TI-201 lung uptake.

Methods

Patient Selection. We retrospectively studied patients referred to our exercise laboratory and identified 25 consecutive patients with exercise-induced increased lung TI-201 uptake and coronary artery disease (group 1). Sixteen additional patients were selected without increased lung TI-201 uptake but a high probability of coronary artery disease by history, electrocardiogram, and stress myocardial imaging (group 2). Eighteen patients (group 3) had normal TI-201 myocardial perfusion, normal lung uptake and a low probability of coronary artery disease by history. Patients with significant valvular heart disease were excluded from this study. For the selection of the normal group (3), patients were excluded if they failed to achieve 85% or more of the age-predicted maximum heart rate despite the presence of a normal TI-201 image.

Stress Protocol. All patients underwent a standardized Bruce protocol (14) exercise treadmill test with a 12-lead electrocardiogram before, during, and after exercise. Patients continued exercising until achieving 85% of maximal predicted heart rate, limiting symptoms, hypotension, or positive ST segment changes. The electrocardiogram was interpreted as positive when there was 1 mm horizontal or downsloping ST segment depression lasting 0.08 seconds (reference isoelectric line is a straight line joining three consecutive P-Q junctions).

Thallium-201 Myocardial Perfusion Imaging. During the same testing session in which the exercise electrocardiogram was performed, we injected 1.5 to 2.0 mCi of thallium 201 (as thallous chloride) intravenously within 1 minute of maximal exercise, and exercise was continued for at least 30 seconds thereafter at the same or slightly reduced workload (15). Each patient underwent imaging in the supine position 5–10 minutes after exercise and again 3 hours later (delayed rest) (16) using an Ohio Nuclear (Technicare) series 120 gamma scintillation camera, a general all-purpose parallel hole collimator with a 20% window centered on 69keV. We obtained the following images: 45° left anterior oblique, anterior and left lateral views, to a total of 500,000 counts per image. Each image was recorded on a Kodak SO-179 film in unprocessed analog form and also in digitized contrast-enhanced form from the video display of an Ohio Nuclear Series 150 Data System.

Image Interpretation. Interpretation of thallium scans was done by two experienced observers without knowledge of patient history or grouping. Thallium scintigrams were read in both analog and contrast-enhanced digital images for the presence of myocardial perfusion defects and increased lung uptake in both the exercise and delayed-resting studies. Lung thallium was qualitatively read as increased if the uptake in the region of interest corresponding to the lungs in the anterior projection was increased over that of the mediastinal area, similar to the method of Boucher (9) (Fig. 1). Interobserver agreement was present in 56 of 59 patients (95%). Agreement was reached by consensus with a third reviewer on the remaining three patients. The myocardial perfusion image was read as equivocal when a consensus could not be reached.

Variables for Comparison. The three patient groups were compared for age, resting heart rate and blood pressure, maximal exercise heart rate and blood pressure, maximal heart rate divided by predicted maximal heart rate, and duration of exercise, using one-way, two-tailed analysis of variance. Sex distribution, prevalence of smoking, beta-blocker therapy, and prevalence of symptoms of dyspnea, fatigue, and chest pain by history and at the time of stress TI-201 were compared by chi square test.

Results

There was no difference in mean age between groups 1 and 2 (Table 1). The mean age of group 3 was significantly lower than groups 1 or 2. Sex distribution was not statistically different among the three groups. The prevalence of beta-blocker

TABLE 1

Clinical Characteristics of Patients Undergoing Exercise Testing

Group	No. of pts	Age	% Male	Smoking (% of pts)	β-blocker therapy (% of pts)
1	25	55.9 (±7.5)	80	68	84
2	16	56.8 (±9.6) **	88	62.5 **	62.5 **
3	18	47.8 (±8.7) *	72	27.8 *	0 **

β-Blocker, beta blocker.

* = $p < 0.05$; ** = $p < 0.01$.

therapy or smoking was not different between groups 1 and 2 ($p = 0.12$) but was increased in both groups over group 3.

Mean resting systolic blood pressures were equal in all groups (Table 2). Resting heart rate in group 3 was higher than in group 1 with no other significant differences. With exercise, there was no difference in maximal systolic blood pressures between groups 1 and 2, yet each was lower than group 3. Maximal exercise heart rate was higher in group 2 than in group 1, with group 3 higher than either group 1 or 2. Maximal heart rate divided by predicted maximal heart rate revealed the same pattern. The number of patients achieving 85% of predicted maximal heart rate was highest in group 3 and lowest in group 1 (the same difference was obtained using 80% of predicted maximal heart rate). Mean duration of exercise was higher in group 3 than in group 1, with no other significant differences. The resting double product (heart rate multiplied by systolic blood pressure) was higher in group 3 than in group 1. With maximal exercise, the double product in group 2 was higher than in group 1; group 3 was higher than both.

The patient groups were compared for frequency of localized thallium myocardial defects (Fig. 2). The only difference detected was a higher occurrence of apical lesions in group 1 than in group 2 ($p \leq 0.03$). Of patients in our study with increased lung thallium uptake, all were noted to have myocardial thallium defects as well. The prevalence of anterior myocardial infarction by electrocardiogram was the same in both groups 1 and 2 (24% vs 25%).

The prevalence of historical symptoms as well as exercise-limiting symptoms was compared between groups (Fig. 3). Patients who developed both dyspnea and chest pain were studied for each symptom. The presence of exertional dyspnea by history was significantly higher in group 1 than in group 2 ($p \leq 0.05$), yet there was no significant difference between these two groups for dyspnea as a stress-test-limiting symptom (nor any difference from group 3). Of patients with a history of dyspnea and increased lung thallium uptake, more stopped exercise because of fatigue than dyspnea (8/14 vs 3/14, $p < 0.05$). The presence of chest pain by history (typical or atypical) occurred with equal frequency in all three groups. The incidence of chest pain during the exercise stress test was the same in groups 1 and 2. There were no patients in group 3 who had chest pain at the time of exercise, although two thirds of these patients had chest pain by history ($p \leq 0.01$). Fatigue as an exercise-limiting symptom occurred with equal frequency in all groups, as did fatigue and/or dyspnea (Fig. 4).

Discussion

Increased lung thallium 201 uptake has been studied in both animals and humans. Bingham et

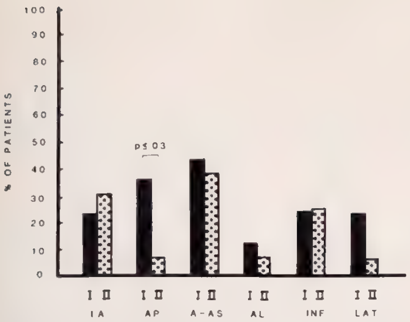
TABLE 2

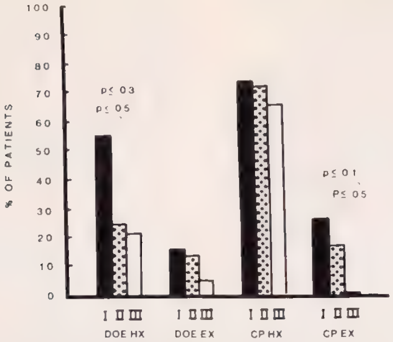
Hemodynamic Parameters of Patients Undergoing Exercise Testing

Group	Rest Syst BP ($\overline{m}$ ± SD)	Max Syst BP ($\overline{m}$ ± SD)	Rest HR ($\overline{m}$ ± SD)	Max HR ($\overline{m}$ ± SD)	Max HR/P Max HR ($\overline{m}$ ± SD)	% Pts Achieving 85% P Max HR	Ex Duration ($\overline{m}$ min)
1	134 (±25)	164.8 (±26.1)	66 (±10.9)	120 (±21.0) *	75 (±13) *	28	5.6
2	128 (±22.5)	170 (±21.7) **	72.9 (±13.7) **	140.7 (±23.7) **	87 (±13) **	56.3 **	6.9 **
3	130 (±17.6)	186.4 (±17.1) *	83.4 (±13.5)	167.7 (±16.3) **	97 (±6) *	94.4 **	8.5

BP, blood pressure; Ex, exercise; HR, heart rate; $\overline{m}$, mean; Max, maximum; min, minutes; P, predicted; Rest, resting; SD, standard deviation; Syst, systolic.

* = $p < 0.05$; ** = $p < 0.01$.





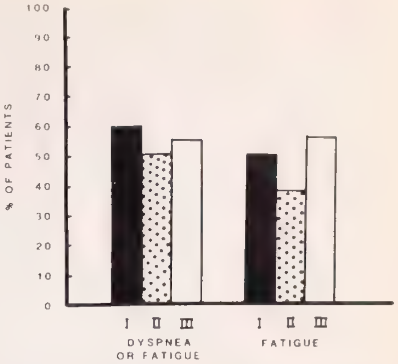


Fig. 2. Left Distribution of thallium-201 myocardial defects on early post-exercise images; 1, group 1; II, group 2; A-AS, anterior or anteroseptal; AL, anterolateral; AP, apical; IA, inferoapical; INF, inferior; LAT, lateral.

Fig. 3. Middle Symptoms by history and at time of exercise testing; I, group 1; II, group 2; III, group 3; CP, chest pain; DOE, dyspnea on exertion; EX, with exercise; HX, by history.

Fig. 4. Right Exercise-limiting symptoms in patients undergoing stress thallium-201 testing; I, group 1; II, group 2; III, group 3.

al (8) demonstrated increased lung extraction fractions of thallium in dogs with balloon obstruction of the left atrium (producing increased mean left atrial pressures and pulmonary transit time). They also studied patients who underwent both exercise testing and cardiac catheterization and showed significant increases in thallium lung uptake in patients with two- and three-vessel coronary artery disease.

Boucher et al (9) studied 227 patients who underwent both exercise testing and cardiac catheterization. Increased lung thallium uptake correlated with an increased number of segmental myocardial thallium defects and increased severity and extent of coronary artery disease. Twelve additional patients underwent simultaneous supine stress thallium imaging and cardiac catheterization. Patients with increased lung thallium uptake had significantly higher pulmonary capillary wedge pressures with exercise than those without increased lung thallium. Kushner et al (11) studied patients who underwent cardiac catheterization within one week of the exercise TI-201 study. Patients with coronary artery disease and increased lung uptake of thallium were found to have significantly reduced resting ejection fractions and more myocardial perfusion defects compared to patients with coronary artery disease and normal lung uptake. Patients with two- and three-vessel coronary artery disease had greater lung uptake of thallium than normals or patients with one-vessel disease.

Similar studies have been performed in post-infarction patients by Gibson et al (10), who studied patients two weeks after myocardial infarction with submaximal exercise myocardial perfusion scintigraphy. This study showed increased lung uptake occurring in patients with a worse clinical history as assessed by the New York Heart classification and a higher Norris coronary artery disease prognostic index. Smeets et al (12) studied 58 patients three months after myocardial infarction with stress hemodynamic measurements and exercise thallium scans. Patients with increased lung uptake had not only a greater incidence of anterior myocardial infarcts, LAD scintigraphic defects, and lower resting ejection fractions, but also higher pulmonary capillary wedge pressures during exercise. In the present study, there is a suggestion of more severe myocardial dysfunction in group 1 than in group 2 because of the greater incidence of apical TI-201 myocardial perfusion defects. Previous work by Gibson et al (10) reported an increased incidence of defects in the anteroseptal and anterolateral distribution.

The common finding of these studies appears to be that increased lung uptake correlates with more significant left ventricular dysfunction and a higher pulmonary capillary wedge pressure with exercise. Gibson et al noted an increased frequency of exercise-limiting "dyspnea or fatigue," but did not separate the two symptoms. There have been no published studies specifically correlating dyspnea alone with lung thallium uptake.

Dyspnea has been defined as "an abnormally uncomfortable awareness of breathing" (13). Patients with left ventricular failure have a reduction of vital capacity as a consequence of replacement of air in the lungs with blood and/or interstitial fluid that has transuded from intravascular to extravascular space. The lungs, consequently, become stiffer, resulting in increased work of breathing. Dyspnea is considered to be a clinical manifestation of pulmonary capillary congestion. Dyspnea occurring with exertion provides strong evidence for the presence of organic disease, such as left ventricular failure (13).

Based on the studies previously described, one might expect patients with increased thallium lung uptake to have a higher incidence of dyspnea at the time of stress testing than those with normal lung thallium uptake. This, however, was not the case in our study. All three groups had similar frequencies of dyspnea at the time of stress testing. On the other hand, dyspnea by history was found with greater frequency in patients with increased lung thallium uptake. Dyspnea by history, then, appears to be a more reliable indicator of left ventricular dysfunction in patients with coronary artery disease than dyspnea recorded at the time of exercise. Of those patients with dyspnea by history and increased lung thallium uptake, more stopped because of fatigue than dyspnea. Reasons for this finding are not clear, although decreasing cardiac output related to severe myocardial dysfunction is one possible explanation. In comparing the type of exercise a patient undergoes on a treadmill test and outside the exercise laboratory, one realizes that unlike exercise encountered in daily life, a treadmill provides constantly increasing workloads. One might expect fatigue to play a more prominent role in this case, particularly in patients who are poorly conditioned, and to occur prior to dyspnea, limiting the frequency with which dyspnea is observed. The incidence of fatigue with exercise, however, was the same in all three groups. In considering dyspnea and/or fatigue, all groups again demonstrated an equal frequency of occurrence.

The intergroup prevalence of chest pain by history was not different between any of the three groups. However, there was an intergroup difference in the occurrence of chest pain at the time of stress testing between groups 1 and 2 compared with group 3. Chest pain with exercise did not differentiate group 1 from group 2 patients and, therefore, seems to be an equally unreliable distinguishing predictor of increased lung thallium uptake in patients with coronary artery disease and, consequently, increased left ventricular dysfunction. Of the patients with a low probability of coronary artery disease (group 3), none had chest pain at the time of exercise (versus two thirds by history). Although chest pain by history does not appear to distinguish between patients with and without coronary artery disease in the current study, chest pain occurring at the time of exercise testing is highly specific for coronary artery disease.

One variable that could not be adequately dealt with in this retrospective study was the incidence of lung disease in patients referred for exclusion of coronary artery disease. Neither arterial blood gas determinations nor pulmonary function testing were performed. The data from the current study is provocative; however, a prospective study is needed that would include such studies.

In summary: Increased thallium 201 lung uptake has been shown to correlate with multivessel coronary artery disease and more severe left ventricular dysfunction. Dyspnea, an expression of pulmonary congestion and a common symptom in patients with left ventricular dysfunction, might be expected to occur more frequently with exercise in patients with increased TI-201 lung uptake. We found that a history of dyspnea on exertion occurs more often in patients who develop increased radionuclide lung uptake after TI-201 stress testing. However, dyspnea at the time of exercise testing does not correlate with this marker of more severe coronary artery disease and left ventricular dysfunction.

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Resistance to Nondepolarizing Muscle Relaxants in a Patient Treated with Ranitidine

Roscoe S. Katende, M.D., and Ivan Dimich, M.D.

Abstract

We report the case of a 30-year-old woman with a history of duodenal ulcer treated preoperatively with ranitidine who underwent abdominal surgery for vagotomy and gastrojejunostomy. Under general anesthesia, she showed profound resistance to three nondepolarizing muscle relaxants. No obvious cause for the resistance was demonstrated except for the possibility of an interaction between ranitidine and muscle relaxants.

Ranitidine Hcl (Zantac) is a potent H-2 receptor antagonist, indicated for treatment of gastroduodenal ulcer. In contrast to cimetidine, it binds weakly to cytochrome P 450 linked oxygen enzyme (1). We report the case of a patient with intractable duodenal ulcer who was treated preoperatively with ranitidine and who intraoperatively experienced extreme resistance to the effect of three nondepolarizing muscle relaxants—D tubocurarine, pancuronium, and atracurium. To our knowledge there is no published data on interaction between ranitidine and muscle relaxants.

Case Report. A 30-year-old woman with an intractable duodenal ulcer was found to have arterial blood pressure 120/80 mm Hg, heart rate 80 beats/min, weight 54 kg. Physical examination, including cardiac, pulmonary, and nervous system, was within normal limits. She reported that her only previous surgery was a tonsillectomy performed when she was three years old with no known complications. Her family history was incomplete; the patient stated that her mother and brother did have some difficulty during anesthesia, but no further details were obtainable.

Vagotomy and gastrojejunostomy were scheduled, and the patient was treated with ranitidine (Zantac), 150 mg twice daily, for three weeks prior to those procedures. She did not receive any other medication and remained otherwise essentially healthy. Preoperative laboratory values, including hemoglobin, hematocrit, blood chemistry (6 and 12 channel), and urinalysis were within normal limits. She was premedicated with diazepam 10 mg an hour and a half before surgery; the last dose of ranitidine, 150 mg orally, was administered with the premedication.

Anesthesia was induced with thiamylal 200 mg and succinyl choline 50 mg intravenously to facilitate endotracheal intubation. Fasciculations were observed and the glottis was wide open. After intubation, anesthesia was maintained with enflurane 1%–2%, nitrous oxide, and oxygen in the ratio 3:2. In addition fentanyl, total dose 200 mcg, was given during surgery. To provide muscle relaxation prior to laparotomy, D-tubocurarine 12 mg was given intravenously. However, because of the lack of response, and the surgeon's inability to retract the abdominal muscles, further doses of 6 mg each were given, totaling 30 mg during a thirty-minute period; furthermore, to document absence of muscle paralysis, the left ulnar nerve was stimulated at the wrist and elbow using a Dig Stim nerve stimulator (Neuro Technology Inc.). The nerve stimulator demonstrated a sustained twitch height with train of four and sustained tetanus at a frequency of 50 Hz, indicating normal muscle contraction and lack of paralysis.

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Pancuronium was then substituted for D-tubocurarine. The initial dosage was 5 mg; this dose was repeated to a total of 14 mg during the following 45 minutes. Once again muscle relaxation was inadequate clinically, and the nerve stimulator showed a sustained twitch height with train of four and a sustained tetanus.

A third agent, atracrium 20 mg, was given, with similar results.

The patient's end tidal ethrane concentration was kept at 2% during the entire surgical procedure to provide some degree of muscle relaxation. Blood was drawn during surgery for measurement of blood gases and electrolytes and were within normal limits; body temperature averaged 36°C. The operation lasted two hours.

At the end of surgery, the patient was still deeply anesthetized, but breathing spontaneously with low tidal volumes. Neostigmine 3 mg and atropine 1.2 mg were given intravenously. In the recovery room, respiration was assisted with a Bird respirator. One hour after the end of surgery, the patient was wide awake and was extubated.

Discussion. This case represents a rare occurrence of profound resistance to nondepolarizing muscle relaxants. Most of the obvious potential causes of the failure of drug action during anesthesia were excluded. Failure of the drug to enter the blood stream was ruled out because the patient had functioning peripheral venous access via a 16G angiocath. Loss of potency of the drug was excluded by the fact that the same batches of these drugs were used successfully on other patients. False-negative muscle stimulation was also ruled out by placing the stimulating electrodes directly over the ulnar nerve at the elbow and wrist.

The relationship between an administered dose of a nondepolarizing muscle relaxant and the resulting degree of neuromuscular blockade is known to be modified by a multiplicity of factors. These include age, acid base status, temperature, pathologic derangements such as burns or lower motor neurone disease (2, 3) and concurrent drug therapy.

Drug interactions described to date generally have involved the potentiation of neuromuscular blockade, most notably antibiotics. Chen et al (4) reported that a patient being treated with phenytoin therapy requires approximately 80% more pancuronium than control patients to maintain a stable level of neuromuscular blockade. Orustan et al. (5) reported resistance to metocurine in patients chronically treated with phenytoin as a result of some yet undefined pharmacodynamic alteration. Azar et al (6) also reported resistance to pancuronium in an asthmatic patient treated with aminophylline and steroids. Azathioprine (Imuran)[7] has also been found to antagonize neuromuscular blockade produced by nondepolarizing muscle relaxants. Meteo et al (8) reported that plasma protein binding affects the free drug levels of D-tubocurarine available to exert pharmacological action. Increased binding of this drug can reduce its effectiveness. Duvaldestin and her co-workers (9) have demonstrated that liver disease increases the distribution volume necessitating more drug—pancuronium—to produce a given degree of blockade.

Since none of the causes described above adequately explains the resistance shown by our patient to developing muscle paralysis following adequate doses of muscle relaxants, it is tempting to attribute the observed resistance to an interaction between ranitidine and nondepolarizing muscle relaxants resulting from some undefined pharmacodynamic alteration.

This case presentation is intended to draw attention to the possibility of drug interaction between ranitidine and nondepolarizing muscle relaxants. Because ranitidine is a relatively new drug, further study is needed to determine what effects, if any, it has at the neuromuscular junction or on the bioavailability of other drugs.

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Environmental Medicine Notes

Alf Fischbein, M.D., editor

Polychlorinated biphenyls (PCBs) are a group of organic compounds almost ubiquitous in the human environment. Although a vast literature details their toxic effects in experimental animals, the risk PCBs may pose to human health has not been well defined. The wide spectrum of clinical abnormalities described in two episodes of acute poisoning following accidental ingestion of PCB-containing rice cooking oil in Japan in 1968 and in Taiwan in 1979 have rarely been observed since, even among workers with long-term, heavy exposure to PCBs. Dermatologic changes and alterations in liver function tests have been reported, as have correlations between PCBs and serum triglycerides and cholesterol levels. The absence of significant clinical findings in such populations is intriguing, since the serum PCB levels of industrially exposed populations have been high in general.

The discovery of the presence of other chemical contaminants such as polychlorinated dibenzofurans (PCDFs) and polychlorinated quaterphenyls (PCQs) in the oil that caused "PCB poisoning" suggests that these contaminants may be important etiologic factors in this clinical syndrome. Studies attempting to clarify the carcinogenic potential of PCBs for humans have not yielded conclusive results to date. Long-term health effects of exposure to the combustion products of PCBs and chlorinated benzenes, including polychlorinated dibenzodioxins, which can be generated in transformer fires, have not yet been clarified.—AF.

Polychlorinated Biphenyls: A Brief Review

ALF FISCHBEIN, M.D., AND JOAN N. RIZZO, M.P.H.

Polychlorinated biphenyls (PCBs) are a group of complex chemicals belonging to the class of chlorinated aromatic hydrocarbons. Because of their chemical and thermal stability, they have been used for many industrial purposes. Their excellent dielectric or nonconductor properties rendered them useful as components in dielectric fluid in transformers and capacitors. They have also been used as additives to paints and surface coatings, in hydraulic systems, and as a constituent in carbonless copying paper.

PCBs have attracted much public health concern because of their low degree of biodegradability and persistence in the environment, with accumulation in biota and human tissues, and because of potential adverse health effects of exposure. The manufacture of PCBs was discontinued in the United States in 1977, and their use has been further restricted. Occupational exposure to PCBs has been controlled so that no worker would be exposed to them at a concentration greater than 1.0 milligrams total PCBs per cubic meter of air (1.0 mg/cu m), determined as a time-weighted average (TWA) concentration for up to a 10-hour workday, 40-hour work week (1–3).

It is estimated that more than 750 million pounds of PCBs are currently to be found in the United States in over 900 million items of equipment. Certain occupational groups may still be at risk of potential exposure, including utility workers handling transformers and capacitors, electricians, appliance service workers, and workers involved in decontamination after haz-

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ardous spills (4–6). Recent PCB-related accidents, especially transformer fires such as the electrical fire in the State Office Building in Binghamton, NY, in 1981, have focused attention on potential health effects to firefighters and emergency crew workers. Note that pyrolysis of PCBs can generate the chemically related and more toxic polychlorinated dibenzofurans (PCDFs), and that pyrolysis of chlorinated benzenes—common constituents in transformer fluid—can result in the formation of polychlorinated dibenzodioxins (PCDDs). These compounds may become of even greater health concern in the future among the occupational groups mentioned (7, 8).

Chemistry and General Toxicity. PCBs are produced by the chlorination of biphenyl hydrocarbons at elevated temperatures in the presence of anhydrous chlorine and a catalyst such as iron or ferric chloride (9). The chlorination results in a biphenyl nucleus in which multiple chlorine atoms are substituted on either or both aromatic rings. Substitution of ring positions by chlorine ranges from dichloroisomers (two substitutions) up to decachloro (ten substitutions) derivatives (Fig.). Commercial PCB mixtures contain several different levels of chlorination and some 100 individual isomers.

PCBs were manufactured in the United States under the trade name Aroclor, and these commercial mixtures are numerically described according to their chlorine contents; for example, Aroclor 1254 and Aroclor 1260 refer to 54% and 60% chlorine content, respectively. The degree of chlorination and specific isomerism have been shown to be related to biological activity and environmental persistence. Likewise, higher chlorinated PCBs tend to be less readily metabolized than PCB mixtures with lower chlorine content. PCBs are lipophilic compounds and accumulate readily in tissues and organs according to adipose tissue content. They have relatively low acute toxicity, but potential chronic or delayed effects are of particular public health concern.

Environmental Contamination. From the beginning of wide-scale industrial manufacturing of PCBs in 1929 to the early 1970s, there were ample possibilities for PCBs to enter the human environment, since no restrictions were placed on either their use or their disposal. Despite such recent regulations, the significant reservoirs of PCBs may still constitute a potential source of exposure to humans. There is no evidence suggesting that PCBs are formed in the environment from natural sources; any environmental presence is therefore a reflection of past human production and use. From a global perspective, the North Atlantic Ocean seems to be a significant reservoir for PCBs, and fresh-water sediment is considered a major continental reservoir. The presence of PCBs in marine organisms in the Atlantic Ocean and other waterways has provided evidence for the ubiquity of PCBs (10). However, the extent of mobilization of PCBs adsorbed to sediment is an important factor that will determine whether the pollution of the marine environment will persist or decrease.

The principal sources of PCBs which have contributed to the present environmental contamination include industrial and municipal effluents. Incineration of paper and other PCB-containing products under conditions which do not destroy PCBs is another potential source of exposure. Release of PCBs to soil primarily from disposal sites with PCB-containing equipment is also thought to be an important source for future exposure, but the assessment of the magnitude of this problem has so far been limited. The release or migration of PCBs is dependent on several factors, including soil structure, soil organic content, and the presence of solvents mixed with or in contact with PCBs. New approaches to the management and control of PCBs and related chemicals in landfills are also urgently needed. Accumulation of PCBs in fresh-water biota has been of particular concern, since fish can be a major source of PCB exposure to humans via the food chain. Several surveys have been conducted of various water sources in the United States, and fish from waters known to have been contaminated with PCBs from industrial wastes in the past were found to exceed the Food and Drug Administration tolerance level of 2 mg/kg. Such water sources include Lake Michigan, the Fox River in Wisconsin, and the Hudson River in New York State (11).

Because of the ubiquity of PCBs in the environment and potential magnification in the food chain, PCBs are present in most humans. In the United States, a serum PCB level of 10 ppb or less is commonly found in individuals without any specific occupational or environmental source of exposure. Significantly higher concentrations have been reported among persons who frequently consume fresh-water fish from waters contaminated with PCBs, but these levels have not been related to any adverse health effects. Although the implications are uncertain, it should be noted that PCBs are also detected in breast milk (12).

Experimental Animal Studies. Numerous animal studies have demonstrated a wide spectrum of

PCB-related toxic effects on various organs and metabolic pathways, including the liver, immune function, reproductive function, and lipid metabolism. Considerable difference in sensitivity to PCBs has been found in various animal species, and animals that are more sensitive to PCBs are usually also more sensitive to the related compounds PCDFs and PCDDs (13, 14). Moreover, the degree of halogenation and position of the halogen atoms is also related to the toxicity of PCBs (15).

One of the major biochemical effects of PCBs is the induction of microsomal enzymes in the liver, which precede other toxic manifestations. Inducers of microsomal or drug-metabolizing enzymes are divided into two main classes. The induction of cytochrome P-450 is associated with increases in activities of ethylmorphine-N-demethylase and aniline hydroxylase, whereas induction of cytochrome P-448 is associated with induction of benzo[α]pyrene hydroxylase activity. The two classes of inducers are also associated with phenobarbital and 3-methylcholanthrene, inducers of P-450 and P-448 respectively. Aroclor 1254 has been demonstrated in rats to induce both cytochrome P-450 and cytochrome P-448 systems, probably reflecting the complexity of isomers and congeners that characterizes PCB mixtures (16). The implications on human health of these PCB-related biochemical effects are uncertain, but drug metabolism studies in humans occupationally exposed to PCBs have documented that these effects may also occur in humans (17).

Dermatologic abnormalities are frequent findings in PCB-exposed animals. The pilosebaceous unit of the skin is the most commonly affected organ. Acneiform lesions are considered quite typical sequelae for PCBs and related compounds. Enlargement of the Meibomian glands and swelling of the upper eyelids are also frequent manifestations associated with PCB poisoning in experimental animals (18).

PCBs have also been demonstrated to produce hepatocellular carcinomas in rodents (19). A wide range of species differences in biological response to PCBs has been substantiated. Therefore, it is uncertain which animal model is the most appropriate in predicting risk of long-term and potentially carcinogenic effects in humans.

Human Health Effects. Despite the widespread industrial use of PCBs, not until 1966 were PCBs first recognized as a major environmental pollutant and identified in both flora and fauna (20). A few reports in the 1930s and 1940s described multiple skin lesions characterized by chloracne, and occasionally systemic health effects in occupationally PCB-exposed individuals. In most instances, exposures had occurred to both PCBs and to other halogenated hydrocarbons, particularly chlorinated naphthalenes (21).

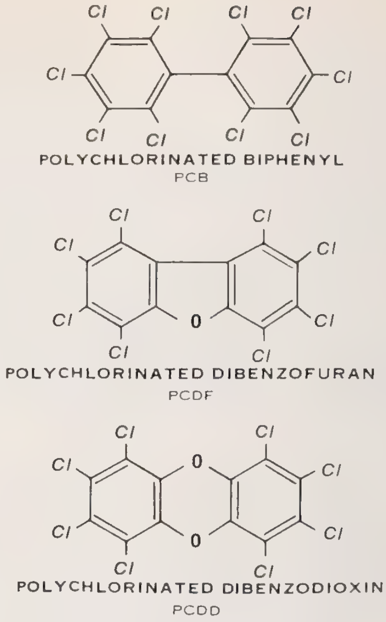

Fig. *Adapted from Letz G. The toxicology of PCBs—an overview for clinicians. West J Med 1983; 138:534–540.*

A clinical syndrome of "PCB poisoning" was first described in detail in connection with two large-scale epidemics that were caused by the accidental ingestion of contaminated rice cooking oil. The first epidemic, *Yusho* (Japanese: "oil disease"), occurred in 1968 in Japan, and the second, *Yu-Cheng* (Chinese: "oil disease"), took place in 1979 in Taiwan. Chloracne, characterized by comedos, pustules and straw-colored cysts, were frequently observed; 60% to 80% of affected individuals had this skin abnormality. Oculodermatologic symptoms were also characteristic of *Yusho* and *Yu-Cheng* and included hypersecretion of the Meibomian glands, palpebral edema, and hyperemia, as well as hyperpigmentation of the conjunctiva (22, 23).

Abnormal liver function tests were reported in severely affected individuals. However, one of the most prominent clinical biochemical findings in both *Yusho* and *Yu-Cheng* was abnormally elevated serum levels of triglycerides. Neurophysiologic examination revealed predominantly sensory neuropathy, although slowing of motor nerve conduction velocity had also been demonstrated, particularly in patients with *Yu-cheng*. Nonspecific symptoms included excessive fatigue, anorexia, and weight loss (22, 23).

Polychlorinated dibenzofurans (PCDFs) and polychlorinated quaterphenyls (PCQs) have been identified both in the cooking oils and in patients with Japanese and Taiwanese "PCB poisoning," and have been suggested as possible etiologic factors in these diseases (24–26).

In contrast to the severe clinical manifestations in patients with *Yusho* and *Yu-Cheng*, investigations of occupationally exposed workers have rarely found clinical abnormalities of similar severity. Abnormal liver function tests and occasional dermatologic abnormalities suggestive of chloracne have been reported in a few studies. Most have been unable to detect clinical effects in workers, despite long-term exposure and the presence of serum levels of PCBs higher than those found in *Yusho* and *Yu-Cheng* patients. Dose-response relationships have not been well elucidated in human studies, even though some biochemical parameters, such as serum triglyceride levels, have shown statistically significant correlations with serum levels of PCBs. Similar observations have been reported with regard to liver function tests, but in most cases the biochemical variables have been within normal range (27–33). Confounding factors have often not been considered.

Other PCB consequences, including adverse reproductive and immunosuppressive effects as well as abnormalities of the endocrinological system, have not been well documented in occupationally exposed subjects. Nor have the suspected carcinogenic effects; mortality studies of occupationally exposed workers have been inconclusive (34, 35), although some have demonstrated a trend toward increased mortality in cancer (36).

Medical Surveillance. Despite the absence of well-established dose-response relationships of PCBs to human health effects, information from studies of occupationally exposed populations suggests the following general guidelines for a medical surveillance program.

1. **Dermatologic examination:** This should focus on examining for the presence of comedos, papules, pustules, and straw-colored cysts consistent with chloracne. The locations of the acne lesions differ from that in acne vulgaris. They are often found behind the ears and on the trunk, thighs, or genitalia.

2. **Liver function tests:** Despite the nonspecific and insensitive nature of such clinical biochemical tests (gamma-GTP, SGPT, SGOT, alkaline phosphatase, and bilirubin) they are frequently used as screening tests. Alcohol history and history of drug use should be considered in evaluating the results of liver function tests. The usefulness of these tests can be increased when the individual serves as his or her own control in serial tests.

3. **Serum lipids:** Measurement of serum cholesterol and triglycerides are useful procedures in general health maintenance, and may be of additional significance in PCB-exposed individuals. Serum lipids should be measured in the fasting state, and it is important to obtain appropriate controls for lipid measurement so that valid comparisons can be made. Fractionation into high- and low-density lipoproteins has been suggested in evaluating occupationally exposed groups, since a decrease in high-density lipoproteins has been reported among PCB-exposed workers (28). It is not feasible to interpret available data on serum lipids in terms of dose-response relationships.

4. **Evaluating exposure and absorption by measuring serum levels of PCBs:** Several laboratories in the United States perform analysis of PCBs in serum, which provides a good indicator of exposure and absorption, mainly through the skin or via the lungs. High serum PCB levels may be present in asymptomatic individuals. The levels measured in an individual or a group of workers are best evaluated in comparison with those found in nonoccupationally-exposed normal controls, who usually have a level of 10 ppb or less of total PCBs in their serum. There are great variations in laboratory techniques, and for serial measurements the same laboratory should perform the analyses.

5. **Measurement of PCDFs** must be performed by a highly specialized laboratory and is not available as a routine toxicologic test. However, the identification of these compounds in serum and adipose tissue might become of greater importance in the future, because of potential exposure from transformer fires in certain occupational groups, particularly firefighters.

6. **Evaluation of the endocrine system, neurophysiologic studies, and immune status** cannot yet be considered part of a battery of routine clinical tests in monitoring of PCB-exposed workers.

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Nonspecific Aortitis and Large-Vessel Arteritis in a 16-Year-Old Girl: CT and Angiographic Diagnosis

A. STOLLMAN, M.D., AND D. MENDELSON, M.D.

Case Report. A 16-year-old girl was admitted to the hospital because of severe abdominal pain. Three months prior to admission she experienced a series of constitutional symptoms that included right temporal headache relieved by Zomax, intermittent sharp midabdominal pain, anorexia, weight loss, night sweats, and pleuritic type chest pain. Examination revealed a left supraclavicular pulsatile mass. A chest x-ray (Fig. 1) at the time of admission revealed a left paraspinal mass which appeared to silhouette the descending aorta.

Although a lymphoma was clinically suspected, the findings on x-ray suggested the possibility of an aneurysm, and the diagnosis of an aortitis was made. She was noted to have microcytic hypochromic anemia, and bone-marrow biopsy demonstrated increased plasma cells and monocytes. A CT scan demonstrated aneurysmal dilatation of the thoracic aorta, the left subclavian artery, and the abdominal aorta below the takeoff of the renal arteries (Fig. 2). An aortogram (Fig. 3) confirmed the aneurysmal dilatation of the descending thoracic aorta, the abdominal aorta below the takeoff of the renal arteries, and the dilatation of the left subclavian artery with occlusion of the left internal mammary artery (Fig. 4). The diagnosis of arteritis was established. Laboratory studies demonstrated negative latex fixation, negative ANA, diffuse hypergammaglobulinemia, and negative VDRL. The patient's echocardiogram and EKG were within normal limits. The patient's HLA typing demonstrated A2, A32, B7, BW6, BW3, DR1, DR2, and MT1. In close follow-up over the following 10 months, the patient demonstrated no onset of symptoms or signs consistent with rheumatic fever or rheumatoid arthritis. There was progressive loss of pulse in the patient's left arm.

Discussion. Many forms of aortitis have been recognized, among them Takayasu's arteritis, giant cell arteritis, and syphilitic and mycotic aortitis (1–4). Aortitis has also been described in association with rheumatic fever, rheumatoid arthritis, ankylosing spondylitis, relapsing polychondritis, and Reiter's syndrome (1, 2). Rare cases of aortitis have also been reported in systemic lupus erythematosis, scleroderma, psoriasis, and ulcerative colitis (1–4).

Based on radiologic findings (1), two basic groups of aortitis have been described: a stenosing variety seen in Takayasu's disease or secondary to radiation in childhood, and a dilating and aneurysmal variety.

The latter may also include Takayasu's as well as others. The findings in our case, of multiple aneurysms with occlusion of the internal mammary artery in a young girl, suggest Takayasu's disease.

Patients with Takayasu's aortitis may have systemic signs that include fever, night sweats, anorexia, weight loss, and malaise as well as symptoms and signs secondary to arterial narrowing and ischemia. The latter manifests as symptoms and signs of aortic coarctation or hypertension secondary to renal arterial narrowing.

The primary pathologic changes in Takayasu's arteritis involve the adventitia and media of the aorta, which early in the course of the disease are infiltrated by lymphocytes and plasma cells. Focal or diffuse disruption of the

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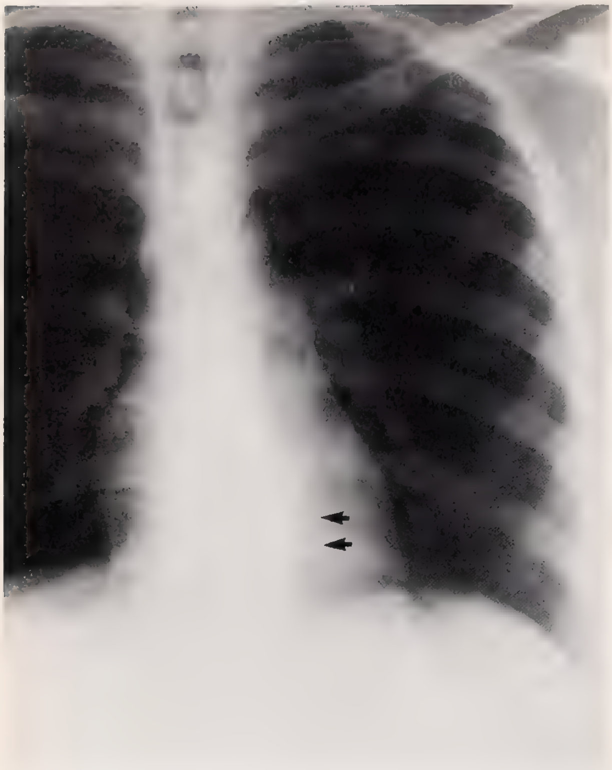


Fig. 1. PA chest roentgenogram demonstrating mass lesion (arrows) silhouetting descending aorta. Paraspinal masses and aortic aneurysm must be considered.

tunica elastica and the muscularis of the media may also be present, and fibrous tissue replacement occurs, with resultant thickening. Although the intima is not initially involved in the inflammatory process, secondary fibrous thickening of the intima does occur.

The etiology of Takayasu's aortitis is obscure. An autoimmune mechanism is, however, considered to be most likely. Recent studies have demonstrated an increased incidence of HLA, A9, MT1, and DR2 in patients with this disease (5). In addition, patients with HLA types BW52 and DW12 are more likely to have active inflammation and rapid progression of disease (6).

The radiographic features of Takayasu's disease have been well described (1, 7, 8). Conventional films of the chest and abdomen may demonstrate dilatation of the ascending aorta or irregular contours and bulging in the descending aorta due to aneurysm-formation. Rib notching may appear due to coarctation, and renal size may diminish secondary to renal arterial narrowing. Dystrophic calcification occasionally occurs in the wall of the aorta. This is fine and pencil-like in outline. However, if secondary atherosclerosis develops, the calcification may be heavy and irregular.

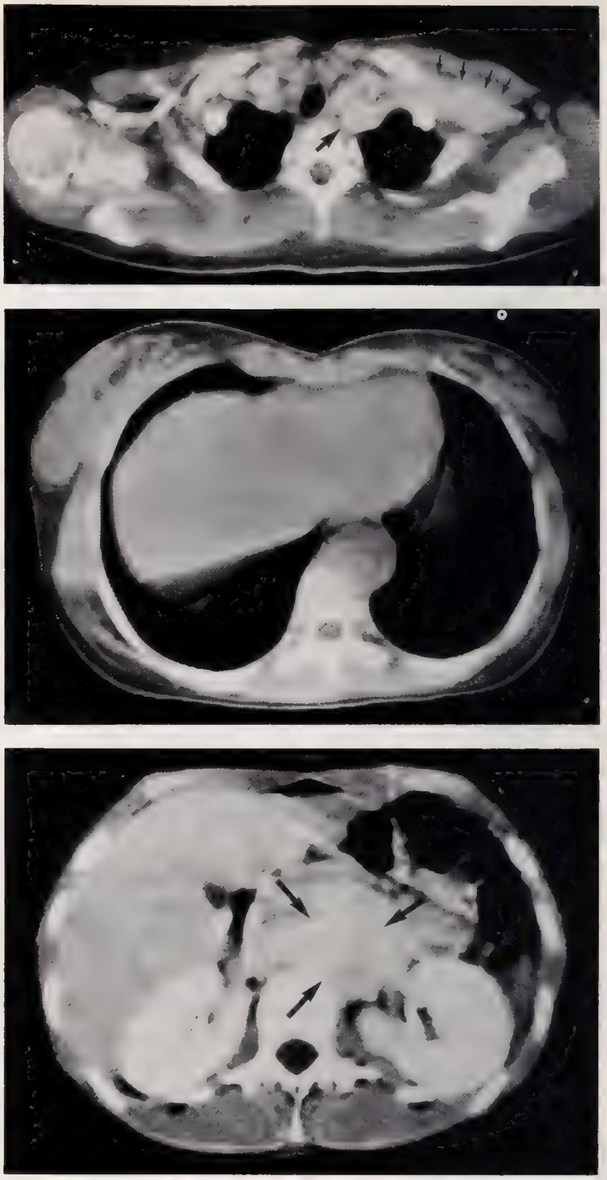
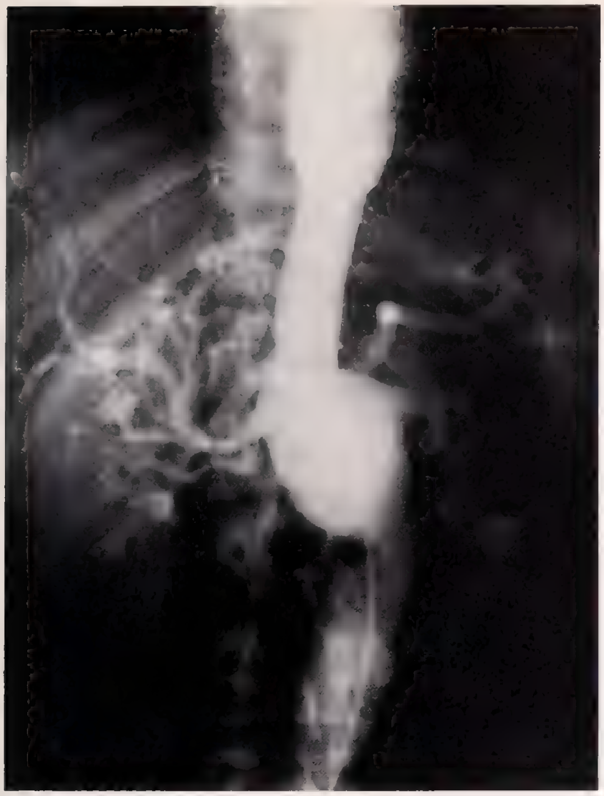


Fig. 2. Thoracic abdominal CT performed after administration of intravenous contrast. Multiple aneurysms are seen. **Top** Image through upper thorax demonstrates marked aneurysmal dilatation of left subclavian artery (arrows). **Middle** Axial image through lower thorax demonstrates aneurysmal dilatation of descending aorta; no paraaortic mass is identified. **Bottom** Abdominal CT image shows aneurysm of abdominal aorta just below renal hila (arrows).

The most common findings on angiography are solitary or multiple segmental areas of narrowing of varying extent. A prominent feature of thoracic coarctation is a predilection for the diaphragm or the region slightly above it. Branch vessels are frequently narrowed or occluded. Aortic regurgitation results from relaxation of the aortic ring or aortic vasculitis. Narrowing of the coronary ostia may cause angina or infarction. Takayasu's arteritis may also cause single



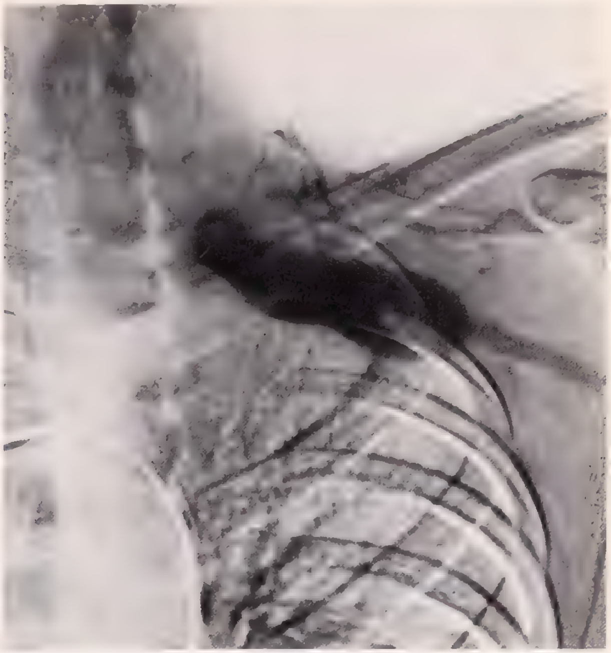


Fig. 3. Left Arteriographic examination of abdominal aorta confirmed presence of aneurysm arising below renal arteries. **Fig. 4. Right** Arteriogram confirms left subclavian aneurysm. Internal mammary artery is occluded.

or multiple aneurysms of the aorta and branch vessels with or without areas of narrowing. The aneurysm formation in Takayasu's arteritis is due to weakening of the aortic wall secondary to inflammation of the media and adventitia. When Takayasu's disease is suspected total aortography is of utmost importance to establish the extent of aortic and branch vessel involvement. Other entities that must be considered in differential diagnoses are giant cell arteritis, syphilitic aortitis, mycotic aneurysm, rheumatic fever, and rheumatoid arteritis.

Giant-cell arteritis is a disease of large, medium, and small arteries. This form of aortitis frequently causes aneurysms of the thoracic aorta. The findings are often similar to those in Takayasu's arteritis; however, the disease usually occurs in older patients (mean age 65 years), whereas Takayasu's occurs primarily in young girls and women. Dissecting aneurysms have been described in giant-cell arteritis but are considered rare in Takayasu's arteritis.

Almost all syphilitic aneurysms occur above the diaphragm and may be fusiform or saccular in configuration. Large ascending aortic aneurysms may cause superior vena cava syndrome or symptoms secondary to tracheal, esophageal, or recurrent laryngeal nerve compression. Aortic insufficiency develops in approximately 60% of patients due to dilatation of the aortic ring or valvulitis. Stenosis of the coronary arteries due to thickening of the aortic intima may occur. Fine, pencil-like calcifications of the ascending aorta occur in approximately 25% of patients. This is similar to that seen in Takayasu's disease.

Mycotic aneurysms may arise intravascularly, as with subacute bacterial endocarditis, or from hematogenous dissemination from a distal site. Aneurysms may also develop from contiguous tuberculous and nontuberculous infections of the mediastinum and retroperitoneum.

The aortitis and arteritis associated with rheumatic fever may be diffuse or segmental, with a predilection for the abdominal aorta. Severe damage is rare, occurring only in recurrent and chronic rheumatic fever. Aortic insufficiency and stenosis are common associated findings.

The rare cases of aortitis in rheumatoid arthritis and ankylosing spondylitis lack sufficient angiographic documentation to compare with Takayasu's arteritis. Aortitis in these entities is usually confined to women and branch vessels are not affected.

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Surgical Pathology Notes

Ira S. Schwartz, M.D., editor

The two cases reported here represent unusual benign stromal (nonepithelial) tumors of the stomach. The vast majority of gastric stromal neoplasms are of smooth muscle origin, both benign and malignant (leiomyoma, leiomyosarcoma). Glomus tumor, a common cutaneous neoplasm, is infrequently encountered elsewhere, the stomach being the second most common site. Fibromyxoma represents a less well-recognized entity of uncertain histogenesis. Stromal tumors of the stomach tend to cause ulceration of the overlying gastric mucosa and may be responsible for massive or chronic upper gastrointestinal bleeding. The recognition of the benign variants affords the opportunity for limited surgery for local excision—ISS

Fibromyxoma of the Stomach

JAISHREE JAGIRDAR, M.D., AND STEVEN DIKMAN, M.D.

Abstract

Benign gastric fibromyxoma is not generally considered in the clinical and radiologic evaluation of a gastric mass or gastric bleeding. The clinical, radiographic, and morphologic appearance of this uncommon tumor may be difficult to distinguish from other intramural gastric lesions.

There have been only eight reports of gastric fibromyxoma following the recognition of the entity in 1925 (1, 2). These tumors are generally not considered in the differential diagnosis of gastric bleeding and intramural gastric lesions. Lack of awareness of this entity may prevent its early recognition.

Case Report. A 64-year-old woman had epigastric pain for several months. Physical examination revealed a palpable epigastric mass. Hemoglobin, hematocrit, and other laboratory values were normal. Gastric roentgenogram following a barium meal showed an ulcerated large smooth contoured mass in the greater curvature of the antrum (Fig. 1). Gastroscopy disclosed a small ulcer at the summit of a smoothly outlined extramural mass which was considered to be a leiomyoma or leiomyosarcoma. Hemigastrectomy was performed.

The excised portion of the stomach contained an 8 × 7 × 5 cm, bulging, soft, smooth mass, 3 cm from the pyloric sphincter. There was a 3 × 2 × 5 cm superficial mucosal ulceration with a smooth margin at the summit of the mass (Fig. 2). On section, the tumor was well circumscribed, homogenous gray-white, soft, shiny, glistening, and entirely confined to the submucosa, distinctly separated from the muscularis. Histologically, the tumor was composed predominantly of stellate cells and loose fibrous tissue with an abundant intercellular matrix composed mainly of mucopolysaccharides (Fig. 3). The patient had an uneventful recovery.

Discussion. Gastric fibromyxomata have been reported in persons aged 27 to 73 years without an age or sex predilection. The tumors were often accompanied by pain, dyspepsia, and anemia that was frequently explained by ulceration of the overlying mucosa. They have been solitary, localized, and sessile, except for one report of a pedunculated fibromyxoma that prolapsed into the duodenum. The greater curvature of the antrum was the most common site (6 of 8 cases) and all re-

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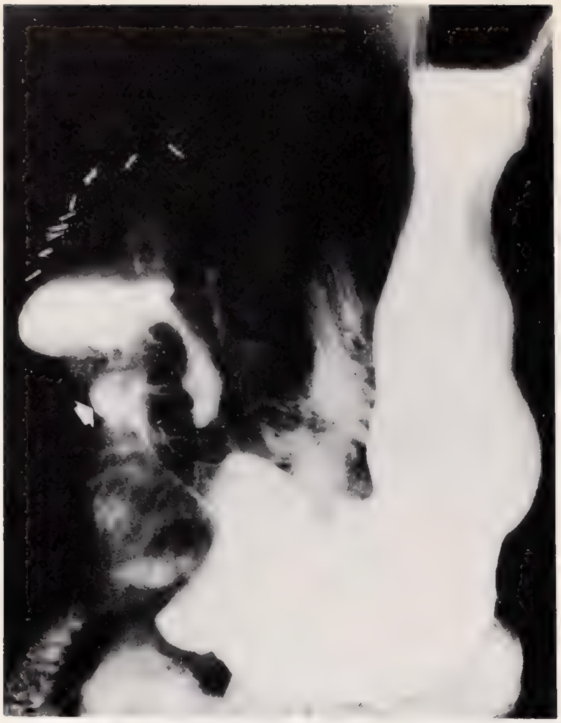


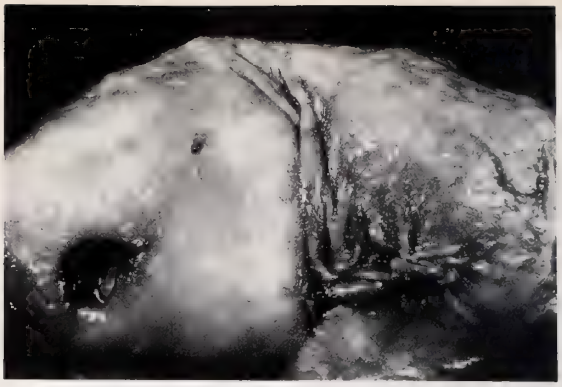
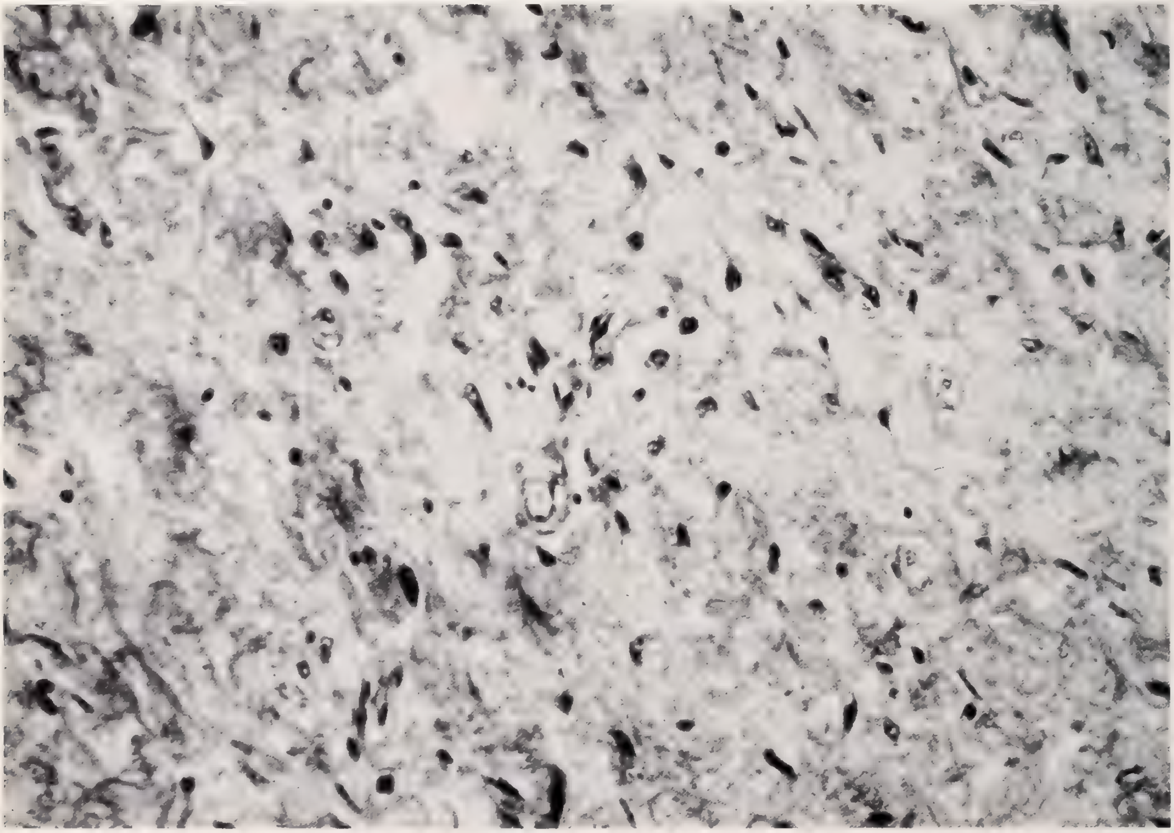


Fig. 1. Left Upper gastrointestinal series roentgenogram showing smooth rounded large mass in gastric antrum with ulcer (arrow).

Fig. 2. Above right Hemigastrectomy specimen with a superficially ulcerated extramucosal, intramural mass.

Fig. 3. Below Microscopic appearance of tumor showing loose myxoid fibrous tissue interspersed with abundant mucoid material (hematoxylin-eosin, original magnification, ×400).



ported tumors were submucosal except for one instance of subserosal tumor (2). The tumors have ranged from 3 to 8 cm diameter. Metastases or local recurrence have not been reported (1, 2).

Radiographic distinction of a gastric fibromyxoma from other intramural lesions such as aberrant pancreas, leiomyoma, neurofibroma, glomus tumor, and other types of gastric fibroma is difficult. The mass produced by aberrant pancreatic tissue, however, is generally smaller than a fibromyxoma and is characterized by a distended central duct orifice. Morphologic distinction between a fibromyxoma and a leiomyoma is not difficult and, in contrast to a fibromyxoma, leiomyomas are usually attached to or within the muscularis. Myxoid areas in the tumor are not unique features of the fibromyxoma and can be seen in other soft-tissue tumors that affect the stomach, such as fibrous histiocytoma, neurofibroma, and schwannoma. Inflammatory fibroid polyps (3) commonly occur in the antrum, and may have myxoid areas. However, unlike the present lesion, they contain a varying mixture of eosinophils, plasma cells, lymphocytes, and histiocytes.

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Glomus Tumor of the Stomach

Dario Caccamo, M.D., Mamoru Kaneko, M.D., and Ronald E. Gordon, Ph.D.

The glomus tumor or glomangioma is an uncommon benign tumor that arises from the modified smooth muscle cells of the glomus body, a neuromyoarterial receptor sensitive to variations in temperature that regulates arteriolar flow. It is most commonly found in the skin, particularly in the nailbeds or fingertips, but it has also been described in many other sites, including trachea, mediastinum, kidney, uterus, vagina, bone, skeletal muscle, and even in a presacral teratoma (1). Approximately 70 instances of this tumor have been described in the stomach but, interestingly, no cases have been recorded elsewhere in the gastrointestinal tract (2). This may reflect the fact that normal glomus bodies in the gastrointestinal tract are present only in the stomach. In contrast to cutaneous glomus tumor, which is usually small and painful, those in the internal viscerae attain a bigger size and are not painful. Those in the stomach are generally symptomatic, inducing ulceration and bleeding (2, 3).

This report describes the histological and ultrastructural features of a gastric glomus tumor and briefly discusses the biological behavior and differential diagnosis of this rare gastric neoplasm.

Case Report. A 79-year-old black woman was admitted to The Mount Sinai Hospital on April 25, 1985 for work-up of chronic anemia and weakness. She had suffered from senile dementia for the last six years. At admission, her hemoglobin was 7.5g/dL and her hematocrit was 22%. White blood cell count was normal but the platelet count was 2,000,000/mm^3. An upper gastrointestinal tract series showed a 4-cm smoothly outlined tumor on the lesser gastric curvature near the antrum and also an irregular, large defect at the duodenojejunal junction. An abdominal CT scan showed multiple hepatic nodules, consistent with metastases. A bone marrow aspirate and a biopsy revealed an abnormally high number of megakaryocytes and no metastases. The thrombocytosis was interpreted as a paraneoplastic phenomenon. At surgery, a 3.5-cm tumor was locally resected from the stomach and a side-to-side anastomosis was performed as palliative treatment for an unresectable tumor mass situated at the duodenojejunal junction, apparently arising in the distal pancreas. A liver biopsy confirmed the existence of a metastatic adenocarcinoma. The patient died four months after surgery. No permission for autopsy was granted.

The surgically resected portion of gastric wall contained a 3.5-cm tumor mass with well-defined borders, ovoid, homogeneous pink-gray, and rubbery. It was sharply circumscribed from the overlying gastric mucosa (Fig. 1).

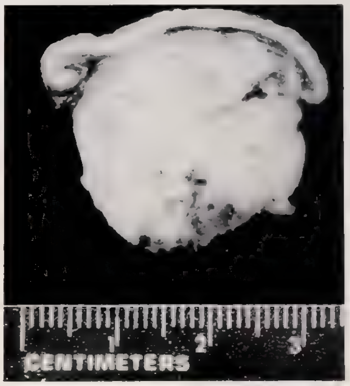

Fig. 1. Cut section of locally resected gastric tumor. Neoplasm is well circumscribed and covered by noninvolved gastric mucosa.

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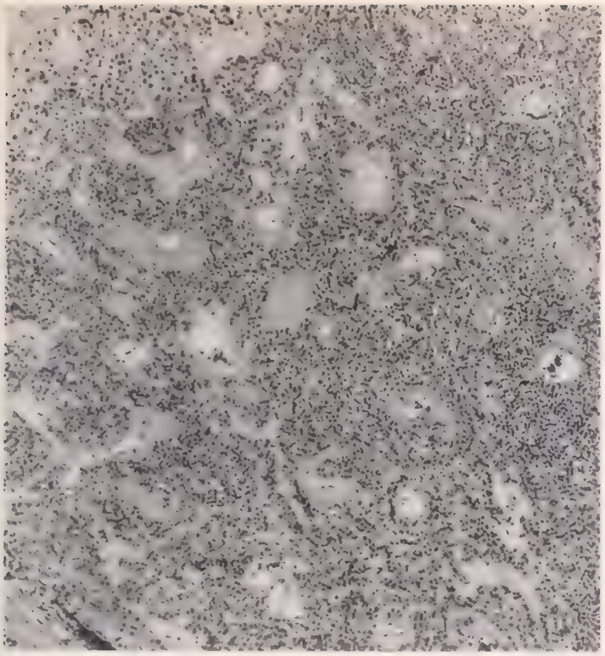
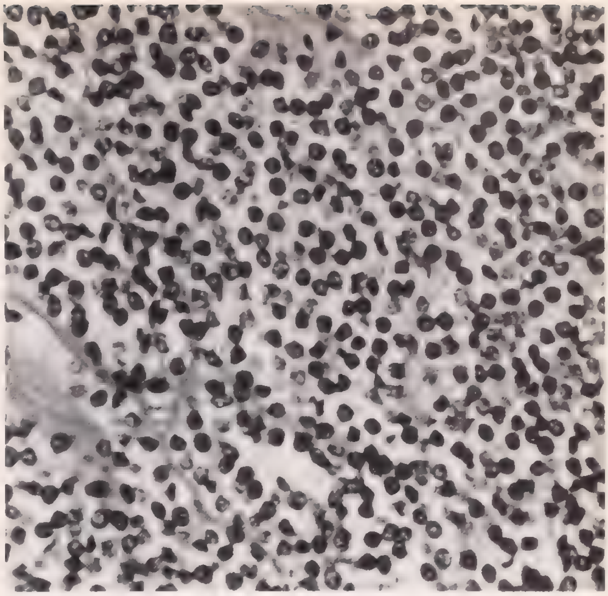




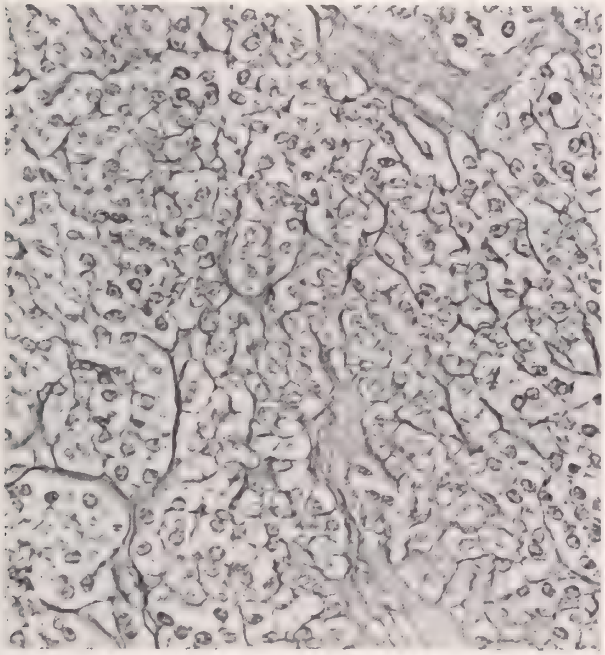


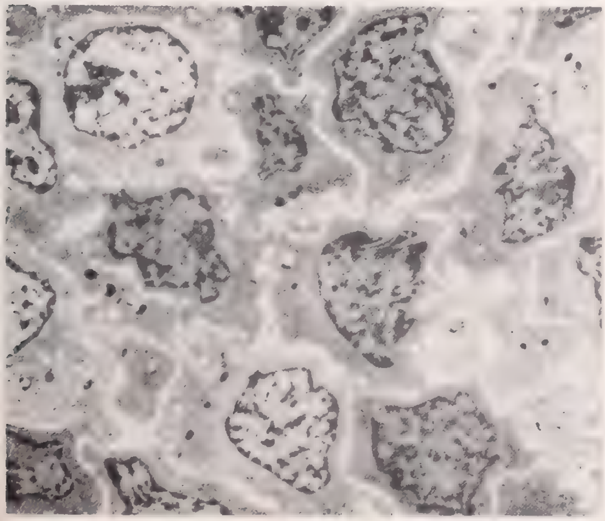
Fig. 2. Top left Low-power view showing sheets of uniform neoplastic cells admixed with numerous thin-walled vessels with perivascular hyalinization (hematoxylin-eosin stain, ×100).

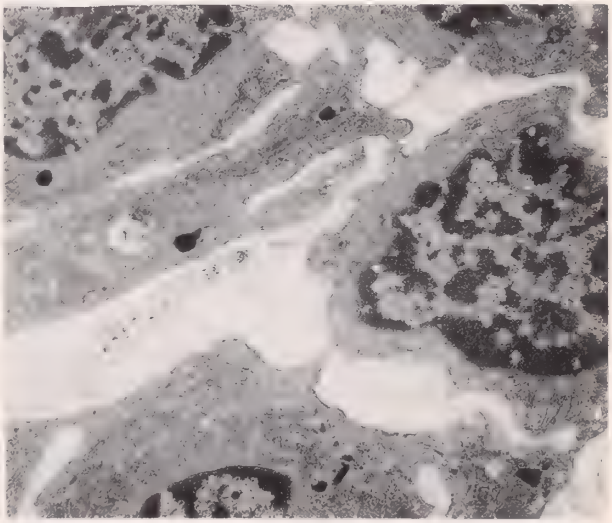
Fig. 3. Top right High-power view showing fairly homogeneous tumor cells with round nuclei containing coarse chromatin. Note absence of mitotic figures or pleomorphism (hematoxylin-eosin stain, ×400).

Fig. 4. Left Reticulin stain depicting reticulin fibers encircling tumor cells in an individual fashion (reticulin stain, ×400).

Fig. 5. Bottom left Low-power ultrastructural appearance of tumor, showing homogeneous population of cells completely surrounded by basal lamina (×3000).

Fig. 6. Bottom right Ultrastructural detail of tumor cells. Note pinocytotic vesicles along plasma membrane and intracytoplasmic myofilaments (×10,000).





Histologically, the tumor was sharply circumscribed but not encapsulated. It was composed of lobules and sheets of remarkably uniform and small oval cells with well-defined cytoplasmic borders (Fig. 2). Nuclei were also uniform with coarsely clumped chromatin. Mitotic figures were absent. One prominent characteristic of this tumor was the richness of vascular spaces, which were generally empty and lined by flat endothelial cells. The lobules and cords of tumor cells were separated by trabecula of fibrous tissue with areas of hyalinization (Fig. 3). Reticulin stain demonstrated fine branching reticular fibers that enclosed glomus cells in an individual fashion (Fig. 4). Grimelius stain for the demonstration of argyrophilic granules was negative. The tumor was situated within the muscularis propria with peripheral large arteries partially surrounded by cuffs of glomus cells. The overlying gastric mucosa was intact and histologically normal.

The electron microscopic study showed the characteristic ultrastructural features of smooth muscle in the tumor cells (Figs. 5, 6), namely basal lamina completely surrounding each cell, electron-dense attachment plaques and pinocytotic vesicles along the sarcolemma and bundles of cytoplasmatic myofibrils entering randomly placed dense bodies. Typically, groups of tumor cells were present along vascular channels lined by endothelial cells and separated from them by a basement membrane.

Discussion. Glomus tumors are thought to arise from the glomus apparatus or Sucquet-Hoyer canal, an arteriovenous shunt associated with blood flow and temperature control. This tumor has been described as an enlarged "caricature" of the glomus apparatus and some authors, such as Murray and Stout, believed that it represented a hyperplastic or hamartomatous process rather than a true neoplasm (4). Glomangioma of the stomach is a rather uncommon neoplasm. In the Department of Pathology of The Mount Sinai Hospital, where approximately 25,000 surgical specimens are processed annually, only three instances of this tumor have been studied in the last 20 years. About 70 cases have been reported in the English-language literature (1–3). The tumor usually arises in the region of the pyloric antrum and attains a size ranging from 1 to 4 cm. Most important, glomangioma has always been benign. Only a single exceptional case of a "malignant gastric glomus tumor" has been reported with metastasis to the liver, lymph nodes, and peritoneum (5): the patient, however, survived more than 15 years after surgical resection of this gastric tumor. Recently, a case of a massive gastric glomus tumor measuring 30 cm in diameter and weighing 12 kg was reported (6) but it was nevertheless benign; the patient died 21 years after surgery, of causes unrelated to the tumor.

TABLE

Histopathological Differential Diagnosis of Gastric Glomus Tumors

Glomus tumor	Lobules of uniform sized cells; conspicuous vascular pattern.
Carcinoid	Organoid pattern; no vascular channels; positive silver stains.
Hemangiopericytoma	Variation in cellular size and shape; mitosis often present.
Leiomyoblastoma (epithelioid leiomyoma)	Variation in cellular size; polyhedral cellular shape; vacuolated cytoplasm.
Lymphoma	Densely cellular tumor; cellular limits nonvisible; frequent mitosis; nuclei may be vesicular or clefted.

From a clinical point of view, the most important symptom of this tumor is gastrointestinal bleeding due to ulceration of the overlying gastric mucosa and the exceedingly vascular nature of the tumor. Endoscopic and radiographic findings are, in most instances, nonspecific, aside from the presence of a gastric mass. Endoscopic biopsy is usually noncontributory due to the intramural location of this tumor. However, one of the cases of gastric glomangioma seen in this department was diagnosed preoperatively, from an endoscopic gastric biopsy which showed nests of typical glomus tumor cells. The pathologist must be aware of the existence of this tumor in order not to confuse it with other benign and, more important, malignant gastric neoplasms, an event that may lead to unnecessarily radical surgery. The main histologic differential diagnoses of gastric glomus tumor are reviewed in the table. Ultrastructural and immunohistochemical evidence (7–9) has been gathered that indicate that glomus tumor, hemangiopericytoma, leiomyoblastoma, and leiomyoma may all be broadly described as smooth-muscle tumors, the glomus tumor appearing to be an intermediate form between hemangiopericytoma and classical leiomyoma. It is probably the only tumor in this broad spectrum of gastric smooth muscle tumors that is practically always benign.

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Methods of Creative Cognition in Medical Diagnosis

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Abstract

Integrating the metaphysical distinctions of analytic and synthetic logic, the scientific method, multiple paradigms of theory fomulation, and various concepts of creative reasoning, a new model of creative medical diagnostic cognition is constructed. This model is operationalized and applied to four classes of diagnostic inquiries. The role of creativity in medicine and its place in medical education is discussed.

The physician must be able to tell the antecedents, know the present, and foretell the future—must mediate these things, and have two special objects in view with regard to diseases, namely, to do good or do no harm. The art consists in three things—the disease, the patient, and the physician. The physician is the servant of the art, and the patient must combat the disease along with the physicians.—Hippocrates (1)

It has often been said, and certainly not without justification, that the man of science is a poor philosopher.—Albert Einstein (2)

The art, science, and practice of medical diagnosis constitute the heart of effective health care. Contemporary medical education stresses the mechanics of diagnostic decision making: techniques of physical diagnosis and history taking, selection of indicated laboratory and special tests, and understanding of pathogenesis. Not surprisingly, the relative deemphasis on orchestrated creative thinking and methods of cognition in medicine reflects the dearth of papers in the literature that examine diagnostic mental processes. Adroit execution of the diagnostic process affords a lucid understanding of the medical problem at hand and favors an unambiguous prognosis and management. The central role of this mental exercise deserves emphasis now, and to this end, a searching assay of the whys and wherefores of thinking in diagnosis is approached here from a philosophic perspective. Discussion of the problem-solving art enlightens us to the challenges of medical inquiry. In addition, a working model of the physician's mind in attacking various clinical problems is proposed.

The Philosophy of Problem-Solving. What is a valid method for the acquisition of knowledge? One may metaphysically distinguish knowledge as analytic or synthetic. For example, the proposition "all patients with Turner's syndrome have the XO sex chromosomal anomaly" is analytic: the predicate ("XO sex chromosomal anomaly") is implicitly contained in the subject ("Turner's syndrome") (3). Whereas the proposition "chlorpromazine administration can cause tardive dyskinesia" is synthetic: the predicate ("tardive dyskinesia") is only one of many possible consequences of the subject ("chlorpromazine administration"). Analytically true propositions are true in all possible worlds conveying no information at all. However, synthetic propositions generate information about the particular system investigated (a patient's psychopathology) within which a specific consequence ("tardive dyskinesia") to a stimulus ("chlorpromazine administration") arises. A more relevant question in medicine therefore becomes: "what is a valid method for the acquisition of synthetic knowledge?" One possibility is objectivity as described by the scientific method.

A cyclic "trilogical" representation of the scientific method consists of induction, deduction, and abduction (4).

Induction is the process of acquiring abstract

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general knowledge about the concrete particulars of experience (4). The inductive conclusion always manifests a greater degree of generality than the evidence on which it is based (4). Furthermore, induction involves the synthesis of knowledge.

Deduction is the process of inferring necessary conclusions from a combination of premises whose truth is either given or assumed (4). Since deductive conclusions are contained implicitly within the premise, if the premises are true, the conclusion must also be true. A deductive hypothesis is arrived at through analysis of a synthetic model. The extent and complexity of analysis depends on the logical sophistication and perspicacity of the scientist.

Abduction consists of the formulation and empirical testing of hypotheses (4). Qualities of a good, verifiable hypothesis include (a) compatibility with other established hypotheses, (b) precision and clarity, (c) fertility in generating empirical data and implying other hypotheses, and (d) simplicity (4). The purpose of the experiment is to demonstrate the reality of the hypothesis in a specific, reproducible manner and is accomplished through proper implementation of the above steps. Data generated from abduction of hypotheses serve as foundation for induction of new models. In medicine, sound ingredients such as accurate history, physical signs and symptoms, and laboratory tests act as substrate for generation of hypotheses (the "differential diagnosis"). Further inducing of pertinent, pivotal notions and subsequent testing lead the physician to a more refined theory (the "principal diagnosis").

The process of theorizing in the scientific method can involve varying relative contributions of analysis and synthesis. In the "model" paradigm of operation, a complete and powerful heuristic guides data acquisition without reciprocal heuristic modification by resultant data (5). Such theory-driven deduction involves analytic logic and is primarily a tool of research. In the "deduction" paradigm, a less formalized, perhaps vapid, network of propositions are repeatedly subjected to and modified by empirical attack (5). Continual alternation of theory-driven deduction and data-driven induction bears a broad conceptualization of phenomena. This process is both a tool and goal of research. The "functional" paradigm resembles the deduction paradigm since it entails both deduction and induction, but emphasizes modest and restricted propositions with short-term interpretation (5). Development of explanatory concepts is closer to a particular experimental problem and therefore provides less scope. Lastly, the "inductive" paradigm is overtly theoretical and goal-directed, consisting solely of data-driven induction (5). It is immune from explicit interpretation and furnishes generalized synthetic principles.

Creativity. The human mind classically depicted by Immanuel Kant functions in four steps: (a) a real object's "representation" is received, (b) the faculty of "sensibility" supplies the manifold "intuition" that creates a corresponding "phenomenon," (c) "understanding" produces "thought," and (d) a net "conception" emerges (6). This process of "sensation" distinguishes the transcendental esthetic of mentation (6).

"Cognition" refers to all the processes whereby sensory input is transduced into mental constructs, used, and stored (7). It involves "intervening variables" which abstract relationships between antecedent and consequent conditions (8). These variables are determined by individual psychological divergences such as motivation and emotion. Cognition may consolidate empirical relationships in the context of a key phenomenon of interest, or innovate mental constructs based on various independent variables. The latter is a creative process by virtue of its inclination toward originality. Creativity consists of preparation, incubation, intuition, and the "aha" experience (9). Computer simulation of creative processes has been accomplished by integrating theory-driven deduction, data-driven induction, and pretheoretical constructs (axioms) to discover novel theoretical terms and properties (9). In short, creativity emerges when psychologic factors stimulate paradigms involving data-driven induction and generation of unique intervening variables. This results in the fabrication of new ideas.

The Diagnostic Mind at Work. Four premises have been presented thus far: the metaphysical distinctions of analysis and synthesis, the scientific method, multiple paradigms of theorizing, and a model of the creative mind. Applying and integrating these premises, one may envision the psychologic substrate for mental diagnostic mechanisms as consisting of four parts: an "A-mode" (analysis); an "S-mode" (synthesis); an operator which determines the paradigm by which the A- and S- modes interact; and a storage or memory compartment (Fig.). The operator sets the level of cognition at which diagnostic decisions arise and is therefore termed the "cognistat." Analysis alone would suffice if a "complete" system of reference facts (unlimited experience and knowledge) existed. Since this is not the case, it behooves the physician to incorporate a synthetic mode of reasoning for difficult cases to determine whether any new ideas are present and necessary for accurate diagnosis. Random autonomous A- and S- mode functioning would be incompatible with intelligent directed thought, so a regulator (the cognistat) is required.

Input to the A-mode can be endogenous or exogenous. Endogenous input originates from the cognistat or storage; exogenous input derives from the external world and consists of the "clinical picture": history, physical, laboratory, pathology, radiology, and so on. The A-mode processes this information using deductive logic, pathognomonic devices ("pearls"), and heuristics ("rules of thumb"). A-mode output flows directly to the cognistat and storage. S-mode input originates from the cognistat and storage. The transduction of A-mode thought into S-mode thought is not via a simple conduit, but rather is mediated by complex mental operations (logical and psychological) directed by the cognistat. S-mode functioning includes induction, classification, pattern recognition, generalization, analogy construction, probable inference, hunches, rational inquiry (leading to the serendipitous discovery), abstraction, imagination, intuition, and even irrationality (due to a discordance between reality and appearance: making the right diagnosis for the wrong reasons). Selection of innovative intervening variables occurs in the S-mode.

Imagination is the process whereby occult constructs in the mind are actively evoked. The unfounded selection of one of these constructs as a tenable hypothesis corresponds to a hunch, but the selection and integration of a set of these constructs into a real solution describes the process of intuition. Abstraction is the process of recognizing features common among a particular group of mental constructs (via selection of intervening variables). The set of features mentally assigned to each construct grows and is refined with experience and education. Thus, in a naive mind, mental constructs are limited, making abstraction difficult. In an educated mind, however, abstraction can make sense of complex interactions and thereby generate elegant models.

Upon termination of S-mode processing, resultant inductions are transferred by the cognistat back to the A-mode for deduction of an appropriate hypothesis. In addition, the synthetic model generated by the S-mode is stored for future reference.

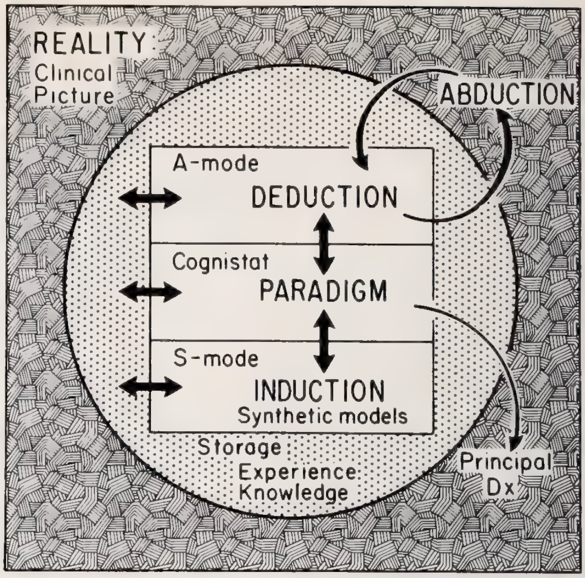

Fig. The human diagnostic mind.

The cognistat has four basic functions: interactive negotiating of A- and S- mode signals, special input from psychologic areas of the mind, special output into a storage area of experiential constructs reserved for future apperception by A- and S- mode operations, and primary output of a theory, or principal diagnosis. The cognistat navigates conscious thought through data-driven induction and theory-driven deduction (9). Interestingly, cognistat functioning can be represented by a "psychic shuttle" commonly employed by artists (10). This entity enables the simultaneous consideration of two extremes during the creative process: realism and nominalism (10). The direction of the shuttle corresponds to induction, if toward realism, and deduction, if toward nominalism. Indeed, medical diagnosis incorporates concepts derived both logically and psychologically like the artist. However, it is the threshold of psychologic satisfaction that delimits the extent to which one pursues truth in medicine. Compromise and reconciliation of the opposing forces of logic and psychology result in the process of "conceptualization" (11). Psychologic satisfaction is based on the conceptual harmony, or consonance, between the signs and symptoms of a patient and the explanatory diagnosis. This happens through exclusion of aberrant data, multiple diagnoses, or a single diagnostic theory elegant enough to explain the entire clinical picture.

Multiple Paradigms of Cognistat Functioning. The cognistat can be tuned to one of four operational settings (paradigms) at one time: deductive, functional, model, and inductive (5). When the cognistat is tuned to the deductive setting, raw empirical data is first analyzed and organized by the A-mode, producing a set of deductive propositions (perceptual preprocessing preceding involvement of the memory compartment). These constructs are shuttled by the cognistat to the S-mode, where an inductive model is created to account for as much of the empirical data as possible. This model of the clinical phenomenon henceforward directs selection of confirming tests and analyses of subsequent data. The cognistat extracts features from the model and shuttles them back to the A-mode where hypotheses are deduced. Furthermore, deduced special tests are implemented to experimentally validate the hypotheses and thereby confirm the model's accuracy. The validated model becomes the principal diagnosis. Throughout, the model undergoes empirical attack that makes verification possible. This paradigm manifests itself solely through deduced confirmation testing. However, the set of tests may intermittently change reflecting model revision.

Case 1: The Deduction Paradigm

Clinical Picture. A 59-year-old woman was admitted in 1965 with a left thoracic mass found on routine chest X-ray. Bronchoscopy at that time was negative. Upper gastrointestinal series was negative. A left exploratory thoracotomy revealed a lobulated mass 10 cm in diameter below the arch of the aorta. Large anterior mediastinal nodes were also seen. A left excisional biopsy of the upper lobe mass and node biopsy showed metastatic carcinoma of undetermined origin. No treatment was given. She was admitted again in 1973 with "viral pneumonia." The chest X-ray at that time showed a mediastinal mass. The patient was treated for the pneumonia and improved. From 1974 on, she began having frequent episodes of diarrhea. Six months prior to her last admission in 1976, she noticed a decrease in weight, malaise, increased facial and periorbital edema, and a cough. Physical examination revealed signs of a superior vena cava syndrome with an anterior mediastinal mass. Hepatomegaly and supraclavicular adenopathy were also found. Electrocardiogram was normal. Laboratory values included hemoglobin of 13.5 g, hematocrit 43.9%, white blood cell count 9100, blood urea nitrogen 29 mg/100 ml, glucose 52 mg/dl, sodium 142 mEq/l, potassium 4.2 mEq/l, chloride 93 mEq/l, calcium 12.8 mg/dl, and phosphorus 1.5 mg/dl.

A-mode. Analysis of clinical features: (a) eleven-year history, (b) hypoglycemia, hypercalcemia, and hypophosphatemia, (c) "superior vena cava" signs, and (d) gastrointestinal symptoms.
Storage.
Cognistat. Suspicion and complexity necessitate shuttling deductions to S-mode.
S-mode. Synthetic constructs: (a) chronicity; (b) G-I symptoms, pancreatic; (c) diffuse benign nature—carcinoid syndrome; and (d) pluriglandular nature—multiple endocrine adenomatosis type-1 (MEA-1) and/or type-2 (MEA-2). Synthetic model: multiple endocrine adenomatosis unlike classic MEA-1 or MEA-2 consisting of parathyroid hyperplasia, pancreatic tumor, metastatic carcinoid, with possible pathologies of the adrenal gland, thyroid gland, and kidney.
Storage.
Cognistat. Extract features from model and shuttle to A-mode.
A-mode. Deduced confirmation tests: workup of thyroid, adrenal, and renal systems.
Storage.
Revised Clinical Picture. Thyroid mass with biopsy consistent with medullary carcinoma; adrenal mass with increased urinary vanillymandelic acid; and small nodule on the right kidney.
A-mode. Analysis of test results: medullary carcinoma of the thyroid gland; pheochromocytoma, and renal pathology.
Storage.
Cognistat. Psychologic satisfaction with consonance between clinical picture and stored model of phenomenon. Principal diagnosis: MEA with metastatic carcinoid.

If verification had not occurred, the initial model would have been grossly revised to account for as much empirical data as possible. Hence, the jerky nature of shifts in diagnostic reasoning characterize this deduction paradigm (12).

The functional setting of the cognistat differs from the deductive setting by its smooth, short-term model refinement (13). This occurs because of a higher threshold for psychologic satisfaction of consonance between the mental representation and the real clinical picture which increases the frequency of model refinement. Mitigating A-mode constructs refine the consonant models that direct necessary supporting tests and data analyses. One recognizes this paradigm by the presence of an initial differential (reflecting a set of deduced hypotheses from the initial synthetic model) that is gradually molded and narrowed down, suggesting new approaches. This eventually furnishes a tentative diagnosis which, after verification, becomes a principal diagnosis.

Case 2: The Functional Paradigm

Clinical Picture. A 44-year-old woman was well until two years prior to admission, when she developed decreased vision in the right eye, and the ophthalmologist made the diagnosis of "pressure on the optic nerve." Her vision progressively improved and she was well until four months prior to admission, when she complained of dizziness and inability to walk. Paranoid ideation was noted concerning her separated husband. She had symptoms of constipation, deepening of the voice, dry skin, puffy hands and feet with acral parathesias, coldness, dry mouth, lethargy, and hair loss. On physical examination, her skin was dry and lemony, the hair was coarse, and the voice was husky. Laboratory values on admission included triiodothyronine uptake of 20.4%, thyroxine by radioimmunoassay less than 1 μg/dl, thyroid-stimulating hormone 64.5 μU/ml, cholesterol 477 mg%, hematocrit 37%; white blood cell count was normal. Lumbar puncture demonstrated 25 lymphocytes, glucose 66 mg%, and protein 94 mg%. Erythrocyte sedimentation rate was 87 mm/hr with a normal complete blood count. Electrolytes and liver function tests were normal.

A-mode. Analysis of clinical features: 1) lethargy/dizziness, 2) primary hypothyroidism, 3) psychiatric disturbance, and 4) neurologic symptoms.

Storage.

Cognistat. Suspicion and complexity necessitate shuttling deductions to S-mode.

S-mode. Synthetic construct: myxedema madness. Synthetic model: primary hypothyroidism causing an agitated behavioral state complicated by infection.

Storage.

Cognistat. Extract features from model and shuttle to A-mode.

A-mode. Differential diagnosis: subacute thyroiditis; Hashimoto's thyroiditis; lymphocytic meningitis; tuberculosis; and CNS tumor. Indicated tests: antithyroid antibodies; computerized tomography of the head; blood culture; and repeat lumbar puncture. Initial treatment: synthroid and thiamine.

Storage.

Revised Clinical Picture. Negative antithyroid antibodies; synthroid improved mentation but not lethargy; negative routine and mycobacterial cultures; suspicion of left posterior fossa space-occupying lesion; and small number of lymphocytes and occasional polymorphonuclear neutrophils in the cerebrospinal fluid.

A-mode. Analysis of test results: exclude Hashimoto's thyroiditis; lethargy not resulting from hypothyroid state; exclude tuberculosis; and CNS pathology not excluded.

Storage.

Cognistat. Psychologic satisfaction not obtained. Shuttle new deductions to S-mode for model refinement.

S-mode. Synthetic constructs: (a) chronicity: slow-acting viral CNS infection, and (b) chronicity: viral thyroiditis. Synthetic model: a slow-acting virus that accounts for primary hypothyroidism and CNS infection (note similarity to first model in this clinical case).

Storage.

Cognistat. Extract features from refined model and shuttle to A-mode.

A-mode. Differential diagnosis: CNS tumor; viral encephalitis; arbovirus, mumps virus, or progressive rubella virus; and subacute thyroiditis: mumps virus, coxsackie virus, influenza virus, ECHO virus, or adenovirus. Indicated tests: thyroid biopsy and look for inclusion bodies; serology; and blood culture.

Storage.

Revised Clinical Picture. Fibrosed thyroid gland and antibodies consistent with mumps virus infection.

A-mode. Analysis of test results: mumps virus infection.

Storage.

Cognistat. Psychologic satisfaction with consonance between revised clinical picture and stored refined model. Principal diagnosis: viral encephalitis and recurrent subacute thyroiditis due to mumps virus infection.

When the cognistat is tuned to the model setting, only A-mode operations work. This paradigm (14) engages for the ordinary routine diagnosis. A very high threshold for psychologic satisfaction, or a psychologic aversion to creativity in medicine, restrain the cognistat from shuttling deductions to the S-mode. Data from the clinical picture simply generate a deductive differential and indicated tests from a stored heuristic. The differential is progressively narrowed down through abduction until a tentative and then a principal diagnosis result. Verification may proceed concomitantly with narrowing down the differential.

Case 3: The Model Paradigm

Clinical Picture. A 42-year-old woman complained of diarrhea, weight loss, and weakness of three months' duration. Stools were described as bulky, foul-smelling, and they "floated." She reported having diarrhea as a child which disappeared as she entered her teens. She had not had previous surgery nor traveled outside the United States. She recently noted easy fatiguability and occasional tingling in her hands and feet. She had transient spasm of her hands with intermittent contraction of her fingers. On physical examination, she appeared pallid and showed signs of weight loss. There was moderate pretibial and pedal edema, and Trousseau and Chvostek signs were positive.

A-mode. Analysis of clinical features: diarrhea, steatorrhea, weakness, weight loss, positive Trousseau sign, and positive Chvostek sign.

Storage. Differential diagnosis heuristic: pancreatitis; Whipple's disease; celiac sprue; collagenous sprue; nonspecific jejunal ileitis; gastrointestinal lymphoma; and secondary lactase deficiency.

A-mode. Indicated tests: gluten-free diet, small-bowel series, pancreatic amylase, stool culture, and lactose breath test.

Storage.

Revised Clinical Picture. Dilated intestinal loops, symptoms allayed with gluten-free diet, normal pancreatic amylase, stool culture indicating bacterial overgrowth, and negative lactose breath test.

A-mode. Analysis of clinical features: celiac sprue not excluded.

Storage.

Cognistat. Psychologic satisfaction with unique diagnosis. Principal diagnosis: celiac sprue.

The induction paradigm has limited purpose in clinical medicine because it lacks abduction steps. The synthetic model generates theoretical propositions that have only academic interest. An example is the etiology of cancer: once clinical data are assessed by the A-mode, the cognistat shuttles deductive constructs to the S-mode, where a model is synthesized in an effort to explain how neoplastic growth occurs. Resultant hypotheses derived from the model might involve viral transformation of the genome or the effects of ultraviolet light on DNA repair. These hypotheses are difficult to verify clinically.

The Role of Medical Education

Tuning the cognistat in medical diagnosis depends on psychologic factors influenced primarily by a physician's training and experience. A young resident might rely more on clinical data, initially employing many heuristic devices and an armamentarium of special tests in order to generate an exhaustive differential diagnosis (model setting), whereas an older clinician might synthesize a differential based on history and physical alone, exclude based on knowledge and experience, and confirm with a minimal amount of testing (deductive setting). Indeed, lack of experience and knowledge by the young physician may predispose to psychologic insecurity (a higher threshold for satisfaction), a reluctance to be creative, and therefore a consuming need to "cover all bases." The unique process of choosing which setting the cognistat will operate by, for a given clinical problem, distinguishes the practice of medicine among individuals, specialties, and cultures.

Traditional medical education serves to develop a physician's database. As the database is filled with more facts, experimental results, clinical images and dialogues, and reasoning experience, cognistat function is modified psychologically. A modern emphasis on creativity would further detection of the more salient aspects of a clinical picture, formulation of accurate synthetic models, and generation of comprehensive yet efficient clinical testing methods. Therefore, the task of the medical professor is threefold: to expose the student to medical information via didactic lectures and laboratories (evaluated by written examination), to promote independent application of learned knowledge on the wards (evaluated by practical examination), and to instruct and encourage appropriate synthetic reasoning techniques (evaluated by oral examination).

Summary

The act of medical diagnosis may proceed as follows: analytic areas of the mind receive and integrate information from the clinical picture, psychologic factors tune the cognistat to a particular paradigm of diagnostic reasoning, and, after a state of consonance is reached, a verified principal diagnosis emerges. Ordinarily, ruling out constituents of the differential assumes the form of questions or specific laboratory requests. But it is directed and purposeful inspection that is the telltale of cognistat functioning and the quintessential element of objective diagnosis.

Individual physician differences may account for differing paradigms of diagnostic approach, yet the endproduct of medicine is judged valid pragmatically, not by the length of time required, nor the energy or finance expended, but when all possible is done to help a patient. One best accomplishes this feat by "understanding" the problem at hand. By harnessing knowledge and experience from the past as well as vision and imagination for the novel, the human mind is the most valuable asset available for medical diagnosis. And even though machinelike logic must correlate a multitude of data describing the clinical picture, an accurate understanding of difficult cases emerges best through coupling of analytic and synthetic reasoning. Diagnosis is therefore a creative process amenable to the challenges of treating each patient as a unique medical situation.

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Student Corner

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Tympanostomy Tubes for Chronic Serous Otitis Media: A Literature Review

ELLIOT GOLDOFSKY, M.D.

Otitis media is among the most common illnesses of childhood (1). Acute otitis media is usually suppurative, but serous middle ear effusions may also have an acute onset. Chronic otitis media with effusion has many synonyms, including such terms as secretory, serous, nonsuppurative, and glue ear (2). The many terms for this illness complicate communication about it. This article uses the term chronic serous otitis media (CSOM).

Many children have recurrent upper respiratory infections, and/or nasal allergy, which increase secretion and produces mucosal edema. The condition is especially severe until the age of seven, because the eustachian tube lumen is small and the nasopharyngeal orifice is surrounded by lymphoid tissue. The lumen may be obstructed by the lymphoid follicles, because in children the tube lies low in the plane of the base of the skull and its cartilages and intrinsic muscles are underdeveloped (3–5). Blocking of the eustachian tube causes negative pressure in the middle-ear cleft which causes serous otitis media. Transudation and bleeding are directly related to the negative pressure, whereas mucosal changes (glandular hypertrophy, edema) have an indirect relation to it.

Management of CSOM requires vast expenditures of time, effort, and money. Aggressive management is based on the beliefs that (a) mild to moderate conductive hearing losses in young children interfere with language development and create an educational disadvantage; (b) the hearing loss will become permanent if untreated; and (c) untreated CSOM predisposes the patient to development of adhesive otitis, ossicular destruction, cholesteatoma and tympanosclerosis (2), all of which result in hearing impairment.

Despite the fears of the possible sequelae of CSOM, treatment of this disease is controversial. Medical management has been shown to be ineffective when compared to placebo (6). Although one million children a year undergo surgery for CSOM, tympanostomy tube (T-tube) insertion has not been shown to be efficacious in a systematic, randomized study. Because of the lack of such a study, we reviewed the literature for the risks and benefits of T-tube insertion in an attempt to aid the physician in management of CSOM.

Management

Forty-one percent of minimally treated Eskimo children displayed permanent structural changes manifested by perforation or significant scarring of the tympana. Of the children with abnormal tympanic membranes, 16% had permanent hearing loss (7). The hearing loss is usually reversible with resolution of the effusion, but permanent conductive hearing loss can result from irreversible changes secondary to chronic inflammation.

Hearing loss is the most prevalant complication and morbid outcome of CSOM (1). To various degrees, fluctuating or persistent conductive hearing loss is always associated with CSOM. Severe, persistent impairment has been shown to have seriously damaging effects on many facets of a child's development. Moderate hearing impairment, if persistent throughout early childhood, may result in impaired language and cognitive function, as well as disturbances in psychosocial adjustment (7–11). However, when hearing impairment is mild, or of relatively short duration, or both (as in the overwhelming ma-

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jority of cases of CSOM), evidence of adverse developmental consequences is lacking (2). Studies suggesting such relationships (12–15) may be considered inconclusive for one of a variety of reasons. The studies were retrospective, small or lacking controls. In particular, subjects were drawn from lower socioeconomic strata, where the chances are greater for the existence of other factors leading to reduced linguistic and scholastic competence.

There may exist in early life critical or sensitive periods during which auditory stimuli and auditory perception must be at optimal levels for full realization of potential. Human studies suggest that even very young infants perceive and respond specifically to spoken language (16). If such critical or sensitive periods exist, and if hearing should be impaired during such periods, it is conceivable that the resulting deprivations or distortions may not be fully compensated later, even if hearing acuity has subsequently been restored.

Patients with serous otitis media in whom antimicrobial therapy has failed (effusion continues for eight weeks) are now thought to have chronic serous otitis media (17). It must now be decided whether to continue medical therapy or resort to a surgical mode of treatment for the patient. In a double-blind randomized trial by Cantekin et al (6), it was found that 34% of those treated with oral antihistamine-decongestant combination had resolution of the CSOM. Yet, it should be noted that antihistamine-decongestants proved ineffective when compared to placebo in the same study.

When considering any therapeutic modality, potential benefits must be weighed against potential detriments. The benefits of myringotomy and tube tympanostomy for the treatment of CSOM are elimination of conductive hearing loss and avoidance of sequelae of CSOM. The T tubes remove the effusion, relieve any associated hearing loss, and maintain middle-ear ventilation. The insertion of T tubes is performed rapidly, and results are usually immediately apparent.

Table 1 lists cure rates of T-tube insertion (18, 21). Rates range from 93% to 75%, with an average of 83%. The divergent results may be explained by differences in surgical technique and the different parameters that each study used to determine the condition of the middle ear. In addition, the observation period seems to be most important. Resolution of disease and improvement of hearing are concomitant with age. Therefore, the benefit of the tubes is difficult to assess over long periods of time, and we do not know whether the outcome would have been significantly different without T-tube insertion.

TABLE 1

Cure Rates of Tympanostomy-Tube Insertion

Barfoed and Rosenberg (18)	93.0%
Schmidt and Van Balkin (19)	84.0%
Shah (20)	80.0%
Smyth et al (21)	75.0%
Average	83.0%

The detriments of T-tube insertion must now be reviewed. Untoward changes in the eardrum following the use of T tubes are common and increase with duration of intubation (22).

Otorrhea may occur after intubation. Herzon (23) noted that 7.9% of his patients developed otorrhea within ten days of T-tube insertion. He admitted that these early infections may be a continuation of the active disease present at the time of surgery, and that the T tube might be serving as a drain. In the same study, an additional 14% of patients developed otorrhea after the first ten days postoperatively. Birck and Mravec (24) reported that 15.2% of ears had ear drainage and 0.6% had to have the tube removed because of uncontrollable infection (Table 2). The importance of this complication is further emphasized when it is noted that 70.8% of otolaryngologists surveyed by Armstrong (26) attributed suppurative otitis media to insertion of T tubes. Naunton reports middle-ear and inner-ear damage as a result of postoperative infections (27).

When the T tube is removed or extruded, tympanic perforations do not always close spontaneously. This complication has been designated in almost all reports as "persistent perforation." The reports limit the definition of perforations that are present and are not treated or healing after six months. McLelland (28) states that the incidence of complications associated with T-tube insertion should be documented in less than six months. Therefore, in his study, a perforation that persisted for six weeks after extrusion was considered a postoperative complica-

TABLE 2

Incidence of Postoperative Drainage

Kokko and Palva (25)	41.0%
Barfoed and Rosenberg (18)	34.0%
Birck and Mravec (24)	15.2%
Herzon (23)	14.0%
Average	26%

TABLE 3

Incidence of Persistent Perforation

Barfoed and Rosenberg (18)	3.0%
McLelland (28)	1.9%
Tos and Poulsen (29)	1.7%
Pappas (30)	0.9%
Birck and Mravec (24)	0.6%
Mawson and Fagan (22)	0.5%
Average	1.4%

tion. This is a sensible observation since it can be argued that even a short-term hearing loss which may occur secondary to perforation may be harmful to the developing child. McLelland (28) obtained a 3.1% incidence of perforation—1.2% healed spontaneously and 1.9% required additional therapy. The incidence of this complication in other series ranges from 3.0% to 0.5%, with an average of 1.4% (18, 22, Table 3).

Another complication of T tubes is that sometimes they need to be reinserted. The tube may be extruded accidentally or deliberately removed and later replaced. Most authors agree that the average duration of the tube in the tympanic membrane is 3 to 18 months. The literature suggests that reinsertion of T tubes becomes necessary in 32% of cases (Table 4).

The incidence of tympanosclerotic changes, another complication of T-tube insertion, increases with the length of follow-up. During a five- to six-year follow-up, Mawson and Fagan report a 30% incidence (22). The range reported in the series is 61% to 15% (18, 29, Table 5). However, it should be pointed out that Mawson and Fagan (22) state that 60% of ears with T tubes showed abnormal appearance following extrusion of the tubes. Some or all of these abnormal tympanic membranes can progress to tympanosclerosis after the observation period.

There are other less common but very serious adverse sequelae of T-tube insertion. A migration of the tube into the middle-ear cavity was reported to occur in less than 0.1% of cases (28). Development of cholesteatoma has also been reported as a complication of T-tube insertion (28), but Pappas (30) did not find this complication in 1,460 cases.

TABLE 4

Incidence of Tympanostomy-Tube Reinsertion

Barfoed and Rosenberg (18)	60.0%
Kokko and Palva (25)	42.0%
Mawson and Fagan (22)	35.0%
Tos and Pedersen (31)	26.0%
Tos and Poulsen (29)	23.0%
Pappas (30)	21.3%
McLelland (28)	14.3%
Average	32%

TABLE 5

Incidence of Tympanosclerotic Changes Secondary to Tympanostomy Tube

Barfoed and Rosenberg (18)	61.0%
Brown et al (32)	42.0%
MacKinnon (33)	33.0%
Mawson and Fagan (22)	30.0%
Tos and Poulsen (29)	15.0%
Average	36%

Conclusion

Lack of uniformity of definition of CSOM and lack of consistency as to what is meant by cure permeate the literature. It has been the attempt of this paper to select those studies which defined cure as that documented by tympanometry. However, even here there was slight variation in evaluating "normal" hearing with tympanometry. The literature also suffered from studies where the age of the population was quite variable, therefore making it difficult to set a standard age for clinical decisions. Follow-up was varied in frequency and/or duration. In addition, no paper in the literature has shown in a randomized study that the T tube is more effective than other treatments of CSOM. While general applicability of these studies is accordingly limited, the physician still must form a plan of management, using the available literature as his guide.

In summary, available otologic and developmental data are insufficient to permit objective judgement as to whether the temporary improvement induced by T tubes outweighs the costs and complications associated with their insertion. T-tube insertion offers approximately an 82% cure rate with complication rates ranging from 1.4% to 36% (Table 6). Mawson and Fagan (22) report a 22% chance of hearing loss in their study of long-term effects of T-tube insertion. Thus, immediate curative results are evident, but adverse

TABLE 6

Complication Rates: Summary

Drainage	26.0%
Perforation	1.4%
Reinsertion	32.0%
Tympanosclerotic changes	36.0%

Each percentage is an average of the incidence of postoperative complications reported in the literature. See Tables 2–5.

sequelae and ultimately auditory deficits may be risks of the procedure. Yet, medical therapy proves ineffective when compared to placebo (6).

What is needed is a prospective, randomized study comparing (a) no treatment, observation of the patient with CSOM, (b) medical treatment, and (c) myringotomy and T-tube insertion. Furthermore, developmental consequences of hearing loss due to CSOM must be studied carefully. The assessment of such potential harm to the child is imperative to justify continued use of T-tube insertion.

Acknowledgments

The author thanks Dr. David Rose of the Community Medicine Department of Mount Sinai School of Medicine (CUNY) for his valuable assistance and encouragement.

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Letters

THE MOUNT SINAI JOURNAL OF MEDICINE
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A Dissent on "Medical Ethics: The Jewish Point of View"

To the editor: A friend has just recently called my attention to the interesting symposium, "Medical Ethics: The Jewish Point of View" (January–February 1984). To the physician, ethics has been important through the ages; and I feel compelled to venture here to express my point of view on the material in this 120-page issue, which records what was said at seven meetings held at the Mount Sinai Hospital in New York City in exchanges between metaphysicians, versed in the preternatural and the supernatural, and physicians, versed in ontology and science. It is apparent that despite several previous encounters, they are still at wit's end to settle problems of medical ethics and morality in our society—perhaps because there is an essential but absent participant, the uninvited patient. The symposium is structured so that an ethical predicament is presented by a physician, and followed by a long, involved comment by a rabbi; a comment that can only be summed up in one word: Faith!

It is difficult to perceive how physicians, trained in the art and science of medicine, can entertain solutions for medical ethical problems based on halakhic laws laid down 2,000 years ago. Ethics are not eternally uniform and constant. It is not my intention to denigrate ancient religious dogma, nor to berate rabbis who dutifully respond in terms of fixed, frozen, immutable ethics and morals once and for all time.

Physicians should recall that Hippocrates (5th century B.C.E.) and Asaph Judaeus (7th or 9th century C.E., Mesopotamia), the earliest known Hebrew medical writer, both skilled ethicists, indicated that it was not gods, but experiences in time and place that dictate ethics and morality for the physician. Concrete knowledge of existing material conditions of life determine the standards by which physicians can formulate their ethics, and not by ancient theological doctrines that can only be a source of religious-ethical encumbrances, confusion, and error.

The symposium starts with the following premises: Jewish tradition, biblical and talmudic commentaries, and writings of rabbinic and medical authorities can be used to advantage "as medical ethics laboriously works its way into a discipline"; medical ethical dilemmas can reveal the common ground among great religions; and ethicists of different cultures and religions possess "the unique ethical and moral thinking that can be applied today." In summary, it is presupposed that ethics and morals derived from God's commandments, the scriptures, etc., can lead to sovereign solutions of modern medical ethical problems. But, ethics and morals are not in a state of rest, stagnant, immutable; they are in continuous change from age to age. Certainly no group has been able, since the beginning of history, to hand out eternal ethics and morals. If this were only true, an overall morality could be achieved, and everyone would know what is evil and bad, and what is right and good. But human history tells a different story.

Judaic writings related sin with illness. The church believed itself right and good in the Middle Ages when it countenanced the cruel oppression of serfs; preached that a "vale of tears" is the "will of God"; and overlooked the abominable practice of *jus primae noctis,* the lord's right to the first night. Religion does not prevent war, poverty, hunger, vice, crime, adultery, incest, murder, prostitution, germ and chemical warfare, nor the promise of the eternal destruction of heaven and earth in a nuclear holocaust. Why, therefore, shall we believe fixed religious doctrines can prevent or solve moral and ethical dilemmas that vary from age to age and nation to nation?

Ethics and morals derive from human social relations concerned with the production of subsistence and the reproduction of life. Of course ethics are different for those who live in a hut and those who live in a palace; for those who are hungry and for those with full bellies; for those with social status and for those with no status; and for those who have special privileges under religion, and for those who do not.

Should physicians apply eternal, unchanging theological doctrines to ethical problems in modern society? Moral sentiments and ethical theories have always been implicit in medicine. It deals with objective reality, and, hence, can find solutions within the context of modern life and its social relations. The principles involved in the development of society in time and place are, in essence, the same as those involved in the development of ethics and morality. In the changes taking place in society, we find the changes taking place in ethics and morality.

Confronted with the ethical problems addressed in this symposium, physicians must consider the welfare, needs, and best interests of those seeking their help within the privileges and rights accorded physicians and patients by society. The state of medical knowledge is not final, but with what it does have, it can make the most advantageous decisions for the patient. Theology can only serve as fetters for the hand and mind of the physician; for there is no straying from its sacrosanct, immutable, relentless, infallible, undeviating doctrines.

I recognize that the rabbis involved in this symposium are of a particular elite group; but at a time when our democratic heritage is reeling under the impact of powerful fundamentalist religious organizations seeking to install prayer in schools, restrict women's rights, denigrate evolution, outlaw abortion, etc., a prestigious medical institution has the dubious distinction of seeking to use traditional religious ethical ideas in the solution of medical ethics and morality. To take a stand against the interference of religion with medicine and the state would certainly be infinitely more rewarding.

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Editor's Note: What this journal publishes is not necessarily endorsed as policy by the institution which is the publisher nor is it necessarily endorsed by the journal itself. Rather we publish what we consider worthy of being added to the pool of ideas that deserve consideration, pro and con, in any debate on the road to action in medical science, with all its social, ethical, and public ramifications.

Authors' Response: The following points in Dr. Bloch's letter deserve comment:

1. The "metaphysicians" include theologians of every major branch of Judaism, orthodox, conserva-

tive, and reform. They are therefore "versed" to varying degrees in the "preternatural and supernatural." The physicians giving their opinions are leaders in several disciplines of medicine—genetics, psychiatry, gynecology, oncology, pediatrics. All participants were attempting to use their experience, background, and tradition to enhance the humanistic aspects of medicine, now an integral part of medical education.

2. Jewish ethicists do not respond in terms of "fixed, frozen, immutable ethics and morals" but rather utilize the unique ethical and moral thinking that can be applied today. Time and place influence human behavior but do not dictate ethics and morality. Objective yardsticks must exist by which people and societies are judged. The Judaic biblical heritage provides such yardsticks. These have been replicated by almost all religions and societies.

3. Examination of the symposium will reveal several examples of medical dilemmas in which Jewish tradition was instrumental in solutions modified for the present "time and place." To highlight just two, see the discussion of neurologic or brain death and of indications for autopsy. A careful reading of these sections will demonstrate that while there is no "straying from the sacrosanct," Judaic "doctrines" have been incorporated and utilized to aid in overcoming present-day medical problems.

4. We are proud that Mount Sinai Medical School, "a prestigious medical institution," is in the forefront of teaching humanistic medicine to medical students, housestaff, nurses, social workers, attendings, and other staff. As part of their endeavors, ethics courses, conferences, and symposia, both at the bedside and in the conference room, are being employed. One source, among many, is the Jewish point of view.

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Pap Smears for Elderly Women

To the editor: Mandelblatt and Hammond (1), after carefully studying the question of taking Papanicolaou smears in elderly women, reported in the Journal that a prevalence rate of 27/1,000 positive smears for carcinoma of the cervix existed in women 65 or older whom they had examined. This rate is much greater than other series yet presented in the literature.

General consensus exists that invasive carcinoma is seen to a greater extent over 65. Sieglar (2) notes the rate is 4.2 times greater over that age and the Massachusetts Department of Public Health (3), 6.3 times greater. These numbers are impressive and are the results of "screening" in the true sense of the word.

Mandelblatt and Hammond did not screen their patients but saw them in an Ambulatory Care Clinic to which patients were frequently referred. The two patients who were responsible for their enhanced rate were seen in the Clinic for postmenstrual bleeding, so that a random quality was not truly present.

When their 200 patients are studied as a whole, the odds ratio of the group over 65 having a carcinoma in contrast to the group under 65 is 1.08 (95 percent confidence levels, 2.2, 0.91). The difference between the two groups under their conditions is not significant. This concept is far different from that derived from the prevalence rate they report on a select small group.

When I screened 3,008 unselected black patients from a poor urban area, I found that the prevalence rate was 1.03/1,000 under 65 and 3.65/1,000 over 65. These numbers are quite comparable with the results of other large series. The odds ratio of having a carcinoma over 65 in this group compared to the individuals under 65 was 3.56 (95 percent confidence levels, 6.44, 1.97).

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1. Mandelblatt JE, Hammond DB. Primary care of elderly women: is Pap smear screening necessary? Mt Sinai J Med 1985; 52:284–290.
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Authors' Response: Dr. Miller's experience that screening elderly women yields more than three times more abnormal Papanicolaou smears than screening younger women is similar to previous reports (1, 2). Seiglar noted that elderly women have a rate of abnormal Pap smears double that of younger women (5.3 vs 2.6/1000) (1). The Massachusetts Department of Public Health reported that elderly women were three times more productive of abnormal Pap smears that women under 65 (6.3 vs 2/1000 respectively) (2). In his letter, however, Dr. Miller has confused the rates with the magnitude of the difference between age groups.

In our pilot study the impact of selection bias was discussed (3). To further assess the need for screening among elderly women, a larger prospective study of all elderly women attending our primary care unit was undertaken. One-quarter of the patients had never had a Pap smear and only 26% had had regular prior screening. As a result of screening, a prevalence rate of 13.5/1,000 (95% confidence interval 5.6 to 21.4) abnormal Pap smears (for malignant and premalignant lesions) was observed (4). This confidence interval range is similar to prior reports.

In our pilot study (3) we reported a prevalence rate of 27/1,000 (95% confidence interval −11 to 65/1,000) abnormal Pap smears in elderly women. The conclusion from the odds ratio Dr. Miller reports from our data for the risk of having an abnormal Pap smear and being over 65 is the same as we presented. Both the odds ratio and our 95% confidence interval include 1 and zero, respectively, that is, neither measure warrants rejecting the null hypothesis that there is no increased risk, or that the true prevalence rate is zero. The confidence interval presents more information (5).

However, we fully agree with Dr. Miller that for certain groups of elderly women, Pap smear screening is beneficial. We look forward to seeing a full report of Dr. Miller's work.

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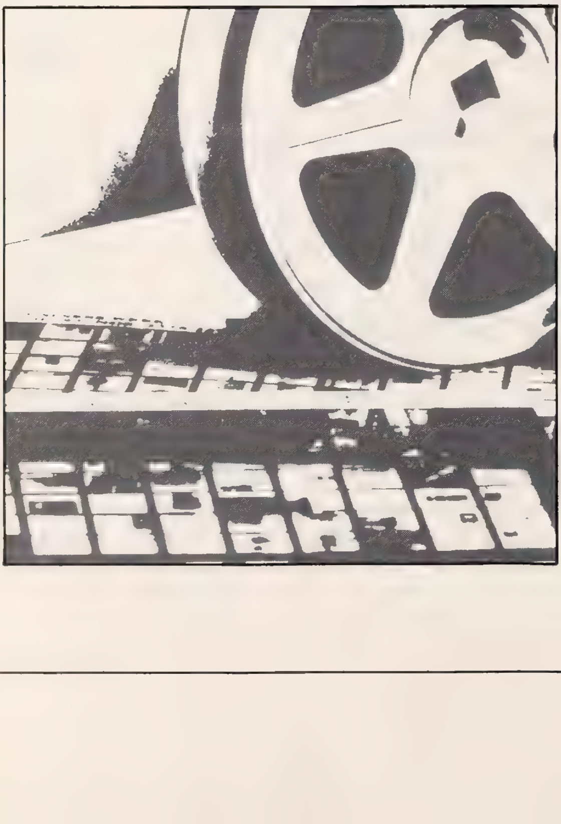

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The Effect of Sham Feeding on Pancreatic Secretion: Preliminary Observations

AMI BARZILAI, M.D., JOSE A. MEDINA, M.D., LEWIS TOTH, M.D., STANISLAW KONTUREK, M.D., AND DAVID A. DREILING, M.D.

Abstract

The increase in gastric secretion following sham feeding presents evidence of vagal pathway for the cephalic phase of gastric activity. No clear-cut data are available indicating the existence of a cephalic phase for pancreatic secretion. We report a study of the gastric and pancreatic response to sham feeding in cervical esophagostomy canines in which gastric secretion was diverted through a cannula. Pancreatic secretion was collected by an indwelling catheter at 15-min intervals for 3 hr before and after (a) cervical esophagostomy, (b) transection of the pylorus and pyloroplasty, (c) parietal cell vagisection, and (d) transthoracic truncal vagotomy. Prior to truncal vagotomy, sham feeding always induced marked increases in gastric flow and acid secretion. Following vagisection, gastric secretion was decreased. Similar, but smaller, alterations were observed for pancreatic flow, bicarbonate secretion, and enzyme production.

These findings confirm a cephalic phase of gastric secretion and indicate the existence of a cephalic phase of pancreatic secretion. The latter response requires an intact vagal system, and any interruption along its distribution will be followed by a reduced response. This cephalic phase of pancreatic secretion is a direct nervous reflux over and above the direct modulation of pancreatic secretion in response to changes in gastric secretory activity and gastrin release.

The increase in gastric secretion following sham feeding presents evidence of a vagal pathway for the cephalic phase of gastric activity, but no clear-cut data are available indicating the existence of a cephalic phase for pancreatic secretion.

Furthermore, Alphin and Lin (1) showed, in the rat, that sham feeding leads to an increase in pancreatic enzyme response only if gastric juice is not diverted.

This study was designed to confirm the existence of a cephalic phase for pancreatic secretion, in the gastric juice-diverted dog, and to determine the vagal pathway mediating gastric and pancreatic responses to vagal stimulation as seen in sham feeding.

Material and Methods

Eight mongrel dogs, weighing between 15 and 20 kg, were prepared with Thomas' type cannuli, one in the most dependent part of the stomach and one in the duodenum, opposite the main pancreatic papilla, after ligation of the accessory pancreatic duct.

All dogs underwent consecutively the following procedures:

1. Cervical esophagostomy—group A
2. Transection of the pylorus and pyloroplasty—group B
3. Parietal cell vagotomy (PCV)—group C
4. Proximal transthoracic truncal vagotomy (TV)—group D

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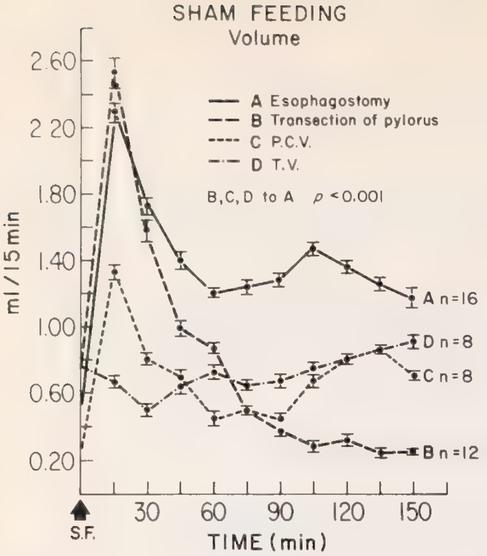


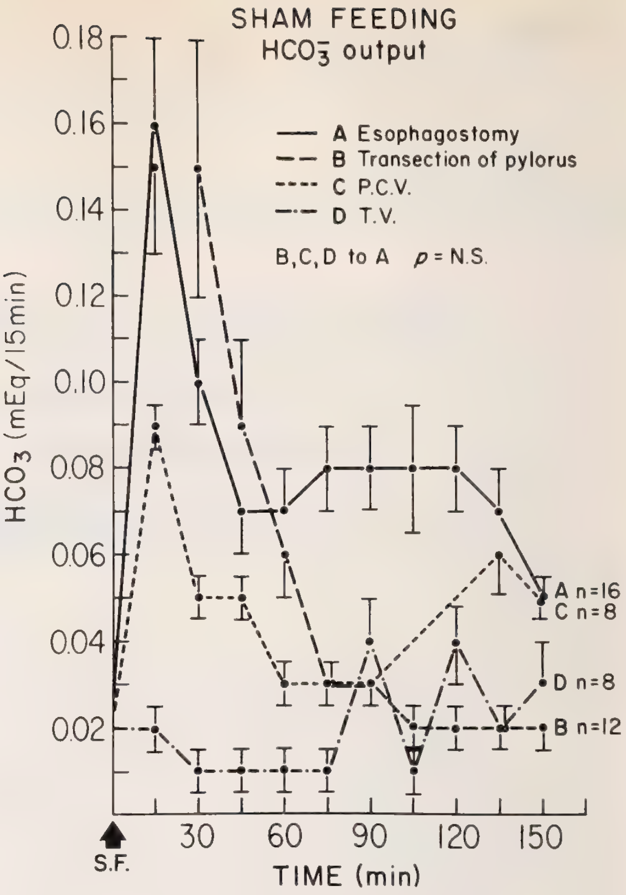


Fig. 1. Left Volume changes after sham feeding, following transection of pylorus (B), PCV (C), and truncal vagotomy (D), with controls (esophagostomy only, A). **Fig. 2. Right** Bicarbonate output (mEq/15 min) after sham feeding, following transection of pylorus (B), PCV (C), and truncal vagotomy (D), compared with controls (esophagostomy, A).

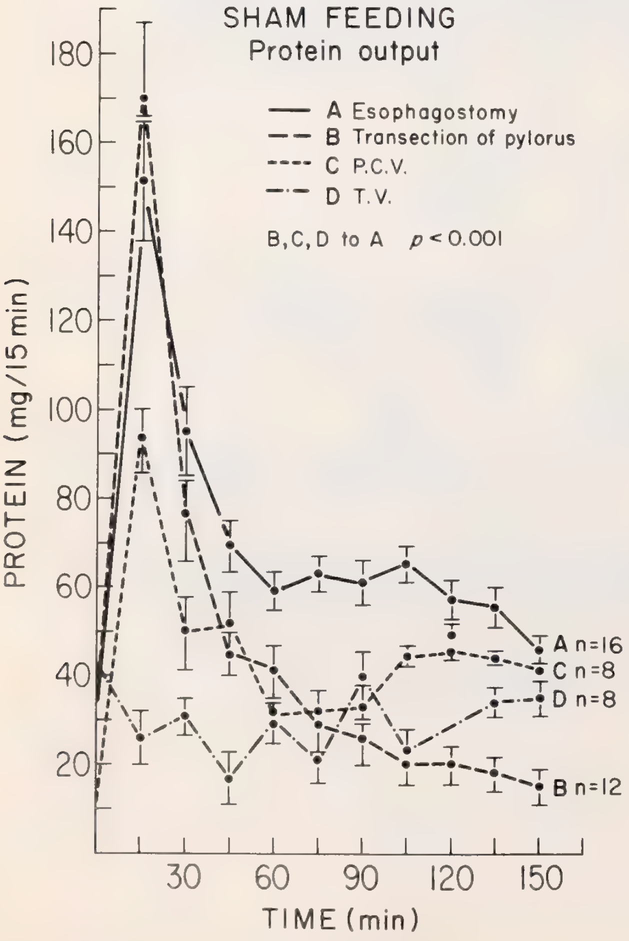
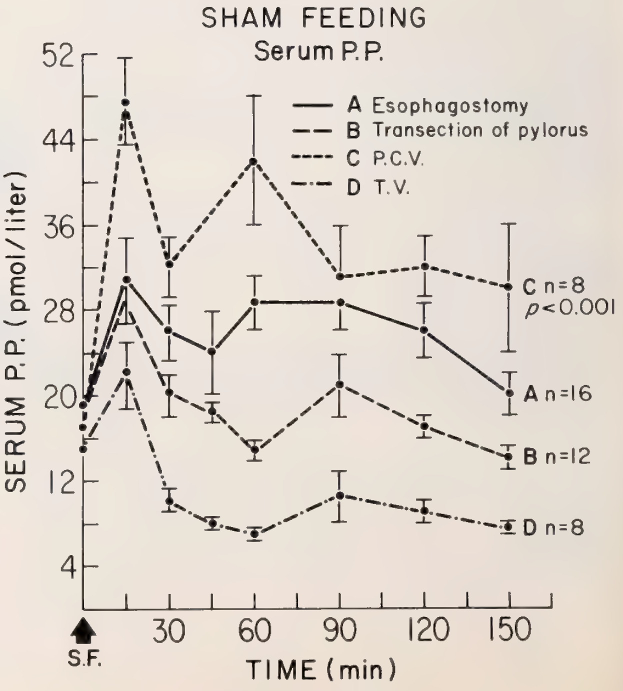


Fig. 3. Left Protein output (mg/15 min) after sham feeding, following transection of pylorus (B), PCV (C), and truncal vagotomy (D), as compared with controls (A). **Fig. 4. Right** Serum PP levels after sham feeding, following transection of pylorus (B), PCV (C), and truncal vagotomy (D), as compared with controls (A).



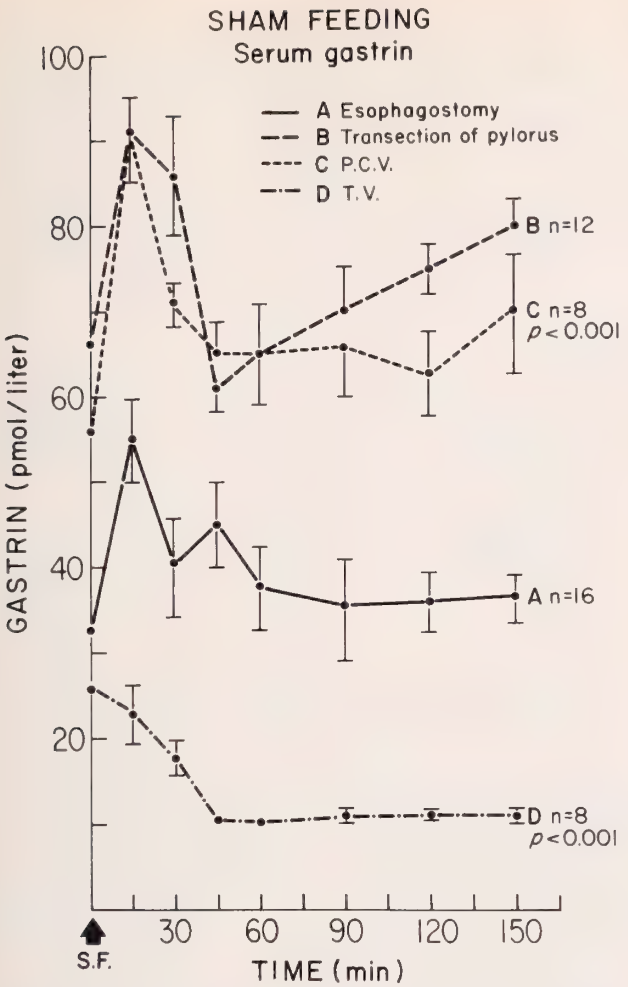


Fig. 5. Serum gastrin levels after sham feeding, following transection of pylorus (B), PCV (C), and truncal vagotomy (D), as compared with controls (A).

After each procedure and 3 weeks of recovery, the dogs were stimulated by sham feeding. The distal esophagostomy orifice was occluded to ensure that no food passed into the stomach.

The gastric cannula remained open during the whole experiment, and all the gastric juice was collected and examined for pH and acid output. The pancreatic juice was also collected for volume, protein enzyme, and bicarbonate concentration, in 15-min intervals. Two or three basals were done first; the dog was then sham-fed continuously for 15 min, followed by pancreatic collections for the next 150 min. Seven blood samples for pancreatic polypeptide (PP) and gastrin were also taken during the experiment.

This procedure was repeated a few times with every dog, following each operation.

Results

Gastric Output. Sham feeding caused a 33% increase in gastric output, as compared with basals in the controls, 680% increase after transection of the pylorus and pyloroplasty, and 250% increase after PCV. Only after truncal vagotomy was acid output reduced by 62.5%. All changes were statistically significant as compared with basal secretion, but only dogs that underwent PCV or TV showed significant reduction of acid output as compared with controls (Table 1). These results are compatible with the extent of the vagotomy performed and confirm the presence of a cephalic phase in gastric secretion.

Pancreatic Output. *Volume* (ml/15 min) was increased in all phases, 150% in the controls, 25% after transection of the pylorus, and 140% after PCV; only after truncal vagotomy was sham feeding accompanied by 9% decrease in volume (Fig. 1).

Bicarbonate output (mEq/15 min) was increased by 170% in the controls, 50% in group B, and 150% in group C, and again only after complete vagisection was there no change as compared with basal (Fig. 2).

Protein secretion (mg/15 min) was increased by 105% in the controls, 4% after pyloric transection, and 300% after PCV. Truncal vagotomy was again associated with decreased secretion of 27% (Fig. 3).

On comparing all phases with the control group, the reduced response in volume and protein secretion was statistically significant, whereas with HCO_3 secretion it was not significant (Table 2).

Notable in the results of blood levels of PP and gastrin following sham-feeding stimulation, after each procedure (Table 3) was a significant increase of PP and gastrin in the PCV group and a significant reduction of both in the TV group (Figs. 4, 5).

Discussion

The cephalic phase of pancreatic secretion was first described in dogs by Pavlov (2), and subsequent studies showed that stimulation of the vagus in anesthetized animals (3, 4) is associated with augmentation of enzyme and bicarbonate secretion (5). The vagal stimulation of pancreatic secretion was especially studied in the dog, where sham feeding produces an increase in enzyme secretion, probably mediated through vagal release of antral gastrin (6, 7).

On the other hand, Alphin and Lin (1) stated that "there is no evidence of a cephalic phase of pancreatic secretion" and that sham feeding leads to an increase in pancreatic enzyme response only if gastric juice is *not* diverted from the stomach. In other words, gastric juice is the

TABLE 1
Results—Gastric Acid Output (mEq/15 min)

Procedure	Basal	Sham feeding	% change	P compared with group A
Esophagostomy	0.81 ± 0.3	3.5 ± 1.0	+330*	
Transection of pylorus	0.57 ± 0.14	4.44 ± 0.66	+680*	NS
PCV	0.02 ± 0.01	0.07 ± 0.03	+250*	<0.001

* Statistically significant.

TABLE 2
Results—Pancreatic

Procedure	Basal	Sham feeding	% change	P compared with group A
Esophagostomy (*n* = 16)				
Volume, ml/15 min	0.57 ± 0.19	1.42 ± 0.36	+150%*	
Bicarbonate, mEq/15 min	0.03 ± 0.01	0.08 ± 0.03	+170%*	
Protein, mg/15 min	35.1 ± 8.7	72.6 ± 30.3	+105%	
Transection of pylorus (*n* = 12)				
Volume ml/15 min	0.63 ± 0.02	0.80 ± 0.76	+25%	<0.001
Bicarbonate mEq/15 min	0.04 ± 0.01	0.06 ± 0.05	+50%	NS
Protein mg/15 min	44.6 ± 0.65	46.2 ± 16.9	+4%	<0.001

* Statistically significant.

TABLE 3
Effect of the Various Procedures on Pancreatic Polypeptide and Gastrin Levels in Blood following Sham Feeding

	Esophagostomy only		Transection of pylorus		PCV		Truncal vagotomy	
	Basal	Stim.	Basal	Stim.	Basal	Stim.	Basal	Stim.
PP, pmol/L								
n	16	32	16	32	8	28	8	28
mean	18.9	27.5	18.3	20.7	16.7	33.6	15.0	10.4
% change	+45*		+18%		+100%*		−30%	
Gastrin, pmol/L								
n	16	32	16	32	8	28	8	28
mean	32.8	40.3	67.6	79.7	55.2	76.3	26.4	12
% change	+23%		+18%		+38%*		−55%*	

* Statistically significant.

specific duodenal stimulus for pancreatic secretion.

Despite extensive study of the regulation of pancreatic secretion during the past 50 years, data available for both humans and dogs are confusing (8–10), and only recently was some evidence provided for direct vagal stimulation of enzyme output in humans (11). Still, there are no clear-cut data regarding a cephalic phase for pancreatic secretion.

The aim of this study was (a) to confirm the presence of this phase, as suggested by Preshaw et al (6), and (b) to elucidate the vagal pathways responsible for pancreatic stimulation during sham feeding. Gastric juice and gastric contents diversion was accomplished by leaving the gastric cannula open during the whole experiment, collecting all gastric juice produced, and applying negative pressure intermittently to the cannula to assure an empty stomach at all times.

According to Tiscornia, the nervous control of the "pancreon," the anatomofunctional unit of the exocrine pancreas, is centered in the intrapancreatic ganglia (12). This small "autonomic nervous brain" is bombarded continuously by impulses derived from "intermediate autonomic nervous brains": two located in the digestive tract, the antral and the duodenal, and one extradigestive, the celiac ganglion. These three autonomic centers appear to be under the influence of the hypothalamic bulbar centers.

Nervous impulses during sham feeding arrive at the pancreas in part directly in the cephalic phase (8, 10), but most pass through the autonomic brains mentioned above. The gastric phase in the neural control of exocrine pancreatic secretion depends on impulses coming from the fundus (4) and from the antrum.

This study was designed so that the vagal impulses would be interrupted at three different levels, starting with the most distal. This was accomplished by transecting the pylorus first and reanastomosing it, thereby interrupting the local branches of the vagus traveling through the pylorus to the duodenum and/or the nervous connections between the antral and duodenal brains. PCV interrupts vagal branches to the fundus, but not to the antrum or duodenum, and transthoracic proximal truncal vagotomy interrupts the main pathway to and from the hypothalamic bulbar centers to the intermediate autonomic nervous brains.

Pyloric transection did not alter the sham-feeding stimulated gastric secretion. However, it is clear from the results that pancreatic secretion of protein is significantly reduced, as compared with controls, as are PP and gastrin levels in the blood (Table 3). This suggests that some of the PP cell secretory fibers do pass through the pylorus to the duodenum. The finding also confirms previous data from this laboratory (13).

Both PCV and TV show reduced basal gastric acid output, but although sham feeding causes 250% increase of acid output in the PCV group, in the TV group acid output is reduced from basal levels by a significant 62.5%. This can be explained by the fact that in PCV there is a selective denervation of parietal cell mass. Although there is little acid in the stomach after PCV, the antral innervation is intact and gastrin production is much increased, as shown by the changes in serum levels of gastrin (Table 3). It is logical, therefore, that sham feeding should cause an increase of acid output in the PCV group. On the other hand, total vagisectomy will abolish gastrin release significantly (Table 3), and sham feeding will be accompanied by a significant decrease of acid output.

Pancreatic secretion after truncal vagotomy is greatly reduced following sham feeding, compared with basal, but only volume and enzyme production are statistically significantly reduced as compared with controls (group A). On the other hand, the PCV group showed a significant increase of volume, bicarbonate, and protein secretion following sham feeding, owing to high levels of gastrin released, as a consequence of low acidity in the stomach and intact innervated antrum and G-cell mass.

It is obvious from our results (Table 2) that the secretion of HCO_3 following sham feeding does not show any statistically significant change after any of the procedures studied. On the other hand, flow and protein secretion are significantly decreased compared with the controls of group A. This change is gradual, and every step in the consecutive denervations is followed by a lesser response of the pancreatic secretion to sham feeding. Sham feeding after truncal vagisection causes decreased secretion of all parameters.

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Among the most intriguing areas of gastroenterology today are the complex relationships between the endocrine pancreas and the gut and between the endocrine and exocrine pancreas. These relationships comprise stimulatory and inhibitory mechanisms as well as positive and negative feedback controls modulating exocrine and endocrine pancreatic function. Progress in the areas can only be accomplished by elucidation of the interaction of the sympathetic, parasympathetic, and peptidergic nervous influences on the gland, detection and identification of long, short, and local reflex arcs involving integration sites in the central nervous system, the spinal cord, the peripheral ganglion, and local nerve plexi, and clarification of the interaction between classical exocrine, endocrine, and paracrine hormones with each other and with the neurons of the autonomic nervous outflow.

We intend to publish a series of articles exploring these complex relationships. Part 1 of the initial paper by Tiscornia and his collaborators presents a total concept as perceived by a seasoned investigator. Although some of the hypotheses may strike some readers as far-fetched or perhaps even wrong, this communication (Part 2 is to be published at a later date) is simply an attempt to integrate known observations, to propose mechanisms, and to stimulate study.—David A. Dreiling

Neural Control of the Exocrine Pancreas: An Analysis of the Cholinergic, Adrenergic, and Peptidergic Pathways And Their Positive and Negative Components

1: Neural Mechanisms

Osvaldo M. Tiscornia, M.D., David A. Dreiling, M.D., Jose Yacomotti, M.D., Rafael Kurtzbart, M.D.,
Alejandro de La Torre, M.D., and Salomon Farache, M.D.

The purpose of this presentation is to review the neural mechanisms that control the secretion, hydrelatic and ecbolic, of the "pancreon" units (1). We analyze the cholinergic, adrenergic, and peptidergic pathways with their positive and negative components and review the afferent pathways, mainly those of pain. At the end we attempt an integrative synthesis based on the concepts of intermediate autonomic brains, "antral," "duodenal," and "celiac"; of vagal sympathetic and sympathetic vagal reflexes; and of the interplay, at the "pancreon" level, between the neuro-endocrine system and the steroid tone imparted by gonadal and adrenal cortex hormones.

Neural Mechanisms: Cephalic Impulses And Gastro-duodeno-pancreatic Reflexes

The main consequence of long and local reflex arcs is the induction and maintenance of an

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From the First Chair of Anatomy, School of Medicine of the University of Buenos Aires, the Centro de Investigaciones Pancreaticas, the Instituto de Morfologia J. Naon, and the Pancreatic Research Laboratory of The Mount Sinai Hospital, New York. Address reprint requests to Osvaldo M. Tiscornia, M.D., at Pozos 1916, 1245 Buenos Aires, Capital Federal, Argentina, or to David A. Dreiling, M.D., Alfred and Florence Gross Professor of Surgery, Dept. of Surgery, Box 1259, The Mount Sinai Medical Center, One Gustave L. Levy Place, New York, NY 10029.

intrapancreatic cholinergic tone. Theoretically, one should also accept an adrenergic and peptidergic tone. However, the cholinergic tone may be accepted as representing the final result of continuous and changing interaction of cholinergic, adrenergic, and peptidergic impulses (2).

The integration of the different nervous impulses to the "pancreon" units and the Langerhans islets is effected in the intrapancreatic ganglion (Fig. 1). It has recently been proposed that the intrapancreatic ganglia and associated nerves act as a pacemaker or as an integration-coordination system to generate oscillation in hormone release from the in vitro canine pancreas (3).

Intrapancreatic ganglia were first reported by Langerhans in 1869. They are in juxtaposition to "pancreon" and Langerhans' islets. The ganglia receive much of the incoming extrapancreatic nerve supply from the vagal and splanchnic nerves. Histologic examination has shown the nerves ramifying from pancreatic ganglia connect both with other ganglia, "pancreon" units, and groups of islets. That the ganglia and associated nerves have some function is suggested by the observation that they do not degenerate but persist after external pancreatic denervation. Thus, to escape atrophy after denervation they must function autonomously.

The pancreatic ganglia are mixed in function because they receive innervation from adrenergic, cholinergic, and peptidergic nerves. They are the embryonic equivalent of Auerbach's and Meisner's plexus in the intestine and function as integration centers to process and distribute local nervous information rather than functioning as simple relays. The intrapancreatic ganglion is like a minute autonomic nervous brain. The pivotal element is the neuron cell. Encircling it are adrenergic fibers that send collaterals, the neurons and peptidergic fibers. Moreover, in some ganglia, interneurons occur rich in dopamine and enterochromaffin cells that store serotonin (4–7). The cholinergic neurons receive cephalic impulses from higher vagal centers (nuclei of the anterior hypothalamus and brain stem) through pre-ganglionic fibers. Some of the latter probably have their origin in the intermediate autonomic nervous brains (8, 9). The latter include two localized in the digestive tract, the "antral" and "duodenal" autonomic nervous brains, and one outside the digestive system, the "celiac" autonomic nervous brain (Fig. 2). The post-ganglionic axons of the intrapancreatic ganglia are distributed mainly to the "pancreon" acinar segment and less densely to the walls of the excretory ducts. Activity of the intrapancreatic ganglia is modulated by adrenergic and peptidergic fibers that encircle them (Fig. 1) (10, 11).

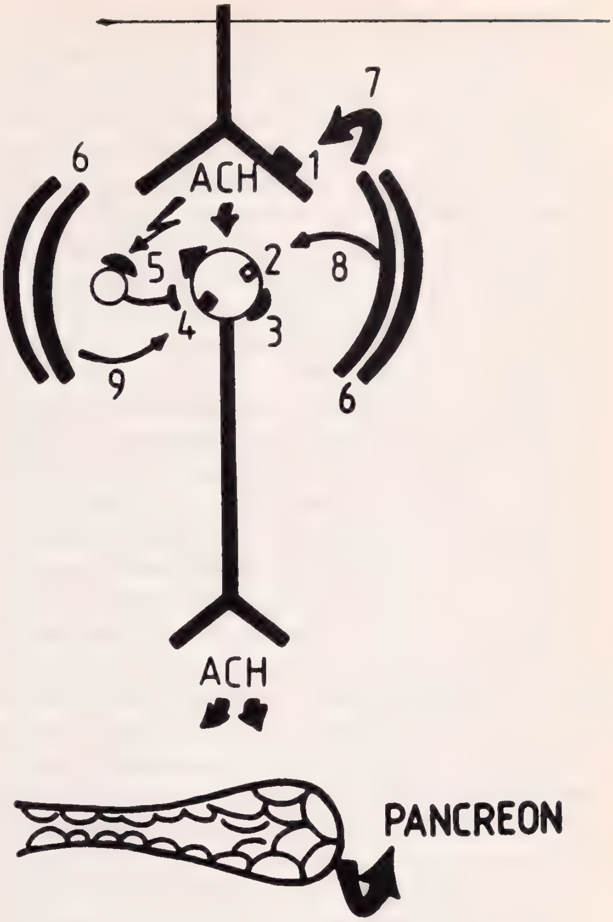

Fig. 1. Hypothetical structure and function of intrapancreatic ganglia. Preganglionic fiber releases acetylcholine (ACh). This neurotransmitter can activate nicotinic (5) and muscarinic (3) receptor on ganglion cell. The former is responsible for F-EPSP, the latter for S-EPSP. Acetylcholine can also activate muscarinic receptor on interneuron or SIF. Postganglionic endings of interneuron release catecholamine (dopamine) that will modulate cholinergic transmission through intrapancreatic ganglia by interacting with alpha-adrenoceptive receptor on neuron cell (4). Catecholamine (noradrenaline) released by adrenergic fibers encircling intrapancreatic ganglia (6) modulates cholinergic transmission by (7, 8, 9) activation of beta (2) or alpha-adrenoceptive receptors, located either on preganglionic fiber (1) (alpha-1) or in neuron cell (4) (alpha-2). Peptidergic branch (neurons and fibers) of autonomic nervous system is not represented.

The following constituents should be distinguished in the intrapancreatic ganglia: (a) the pre-ganglionic fiber; (b) the neuron ganglion cell; (c) the small intensely fluorescent cell (SIF) or interneuron; (d) the adrenergic fibers encircling the ganglia and the branches synapsing the neuron cells; (e) the cholinergic and adrenergic receptors on the pre-ganglionic fiber, the neuron and the interneuron cells. The pre-ganglionic fibers release acetylcholine as neurotransmitter. This acts on two types of cholinergic receptors in the neuron cell, nicotinic and muscarinic. The former can be blocked by hexamethonium and similar agents, the latter by atropine. Through the nicotinic pathway, acetylcholine triggers a fast post-synaptic potential (F-EPSP) and through the muscarinic receptor, a slow excitatory post-synaptic potential (S-EPSP). The interaction between the preganglionic fiber and the interneuron is also by means of a muscarinic receptor. The post-synaptic neurotransmitter of the SIF cells is dopamine, which—acting upon an alpha-adrenoceptive receptor of the ganglion cell—elicits a slow post-synaptic inhibitory potential (S-IPSP), slowing or blocking the transmission of the nerve impulse through the ganglia. Dopamine, after eliciting S-IPSP, exerts a selective facilitation of the slow excitatory post-synaptic potential (S-EPSP). This is a long-lasting effect that, once initiated, continues even when there is subsequent interference with dopamine receptor interaction, an effect suggesting a long-lasting metabolic and/or structural change in post-synaptic neuron (10).

The catecholamines released by the adrenergic terminals which encircle the ganglia formations, by acting on alpha-adrenoceptive receptors, located on the preganglionic fiber, block parasympathetic impulses. Recently, presence of inhibitory alpha-2 adrenoceptive receptors has been demonstrated on the neuron cells. These receptors can be activated by clonidine and blocked by yohimbine. Reports of the effects of catecholamines on beta-adrenoceptive receptors are contradictory. In the isolated perfused cat pancreas, isoproterenol, a beta agonist, by release of post-ganglionic acetylcholine, increases amylase secretion (12). In the anesthetized rat, isoproterenol has a hydrelatic effect (13). In contrast, in conscious dogs, this catecholamine, superimposed on a secretin-plus-CCK perfusion, markedly inhibits pancreatic hydrelatic and ecbolic pancreatic secretion (14). It should be noted that sympathetic impulses, in addition to modulating parasympathetic flow, significantly influence intrapancreatic blood circulation. Adrenergic hypertonus induces ischemia through an alpha effect. One mechanism would be opening of arteriovenous shunts, resulting in diminished microcirculation flow (6, 7, 12). Normally, cholinergic impulses are mediated by nicotinic receptors but, under certain conditions such as nicotinic blockade (hexamethonium), decentralization (truncal vagotomy), catecholamine depletion (reserpine), acetylcholinesterase inhibition (ethanol), the transmission of nervous impulses is effected through the non-nicotinic receptors (10, 15).

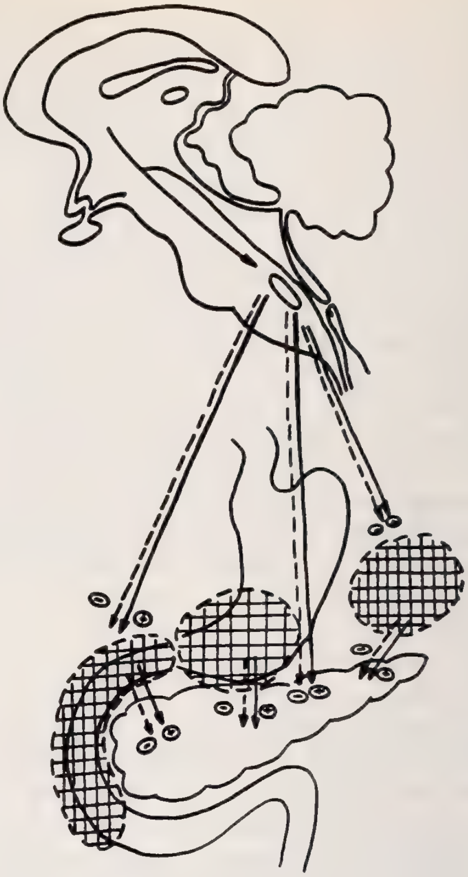

Fig. 2. Hypothalamic-brain-stem modulation (positive and negative impulses) of intrapancreatic ganglia and "intermediate autonomic nervous brains": "antral," "duodenal," and "celiac." The latter also exerts modulating influence (positive and negative impulses) on "pancreon" units, either directly or indirectly through intrapancreatic ganglia.

The intrapancreatic ganglia possess a remarkably rich density of neurons and fibers belonging to the peptidergic or third branch of the autonomic nervous system (16). The peptides involved include VIP (17), somatostatin (19), substance P, enkephalins (19), bombesin (18), and gastrin-CCK-like compounds. For example, vagal impulses release VIP, which promotes an atropine-resistant rate of flow and the secretion of bicarbonate (17). Bombesin release exerts a hydrelatic but preferentially an ecbolic atropine-resistant effect on the exocrine pancreatic secretion (EPS) (18). An anatomophysiologic fact crucial for the interpretation of pancreas innervation is the consideration of two basic components, a positive activation, and a negative inhibition of secretion.

Positive Impulses

We can distinguish positive cholinergic impulses, positive adrenergic impulses, and positive peptidergic impulses.

Cholinergic. Positive cholinergic impulses enhance intrapancreatic cholinergic tone. They may originate in the central nervous system (hypothalamic-bulbar nucleus). This occurs in the *cephalic phase* control of the EPS. The positive cholinergic impulses arrive at the intrapancreatic ganglia mainly via the vagus nerves but also through cholinergic splanchnic fibers (7, 9, 12). Anatomically, by means of the horseradish peroxidase (20), right or posterior vagal trunk at the level of the esophageal hiatus can be shown to be composed of pre-ganglionic fibers of the right dorsal and ambiguus nucleus. Many of these fibers enter the pancreas passing through the celiac ganglion and its branches and generally avoiding the gut wall (antro-pylorus-duodenum). These findings are in contradistinction to previously published studies using the classical method of anterograde axonal degeneration (21, 22). In the rat we have observed that celiac ganglionectomy induces in the head of the pancreas the same percentage fall of choline-acetylase activity (30%) as truncal vagotomy. This finding suggests that the anatomical pathway of cholinergic fibers innervating the head of the pancreas passes primarily through the celiac ganglia (23–26).

The reported observation of alteration of the EPS response to vagal stimulation in the dog following ligature of the pylorus is still controversial. Popielski, a member of the Pavlov school, was the first to show that transection of the pylorus or its stricture by means of a ligature totally suppressed the EPS response normally elicited by the electrical stimulation of the vagal trunks in the thorax (6, 7, 12, 27, 28). This was confirmed by Gayet and Guillaumie (29, 30) in the same animal. The vagal secretory fibers were presumed to course through the subserous layer of the stomach, a supposition suggested by the observation that isolated ligature of the pyloric mucosa does not interrupt the reflex arc. According to Popielski (27, 28) and Gayet and Guillaumie (29, 30), all the pancreatic secretory fibers present in the vagi pass through the pylorus. Popielski (27, 28) stressed that excitation of the vagal hepatic branch does not elicit pancreatic secretory changes. Gayet and Guillaumie (29, 30) emphasized that the vagal secretory fibers enter the stomach in the lower segment of the lesser curvature and that cutting the fibers going to the superior segments of the stomach does not interfere with the pancreatic secretory response triggered by electrically vagal stimulation. The same happens when the lesser curvature is detached for 2 cm at the level of the pylorus. In contrast, detachment of the lesser epiplon between these two segments (the upper third of the stomach and the pylorus), equivalent to a selective antral denervation, significantly depresses the EPS response following electrical stimulation of the vagal trunks. These data indicate participation of the gastric antrum in the control of EPS.

An interesting and still unresolved question is the anatomic pathways followed by pancreatic secretory fibers beyond the duodenum level. According to Popielski (6, 7, 12, 27, 28) these fibers leave the duodenal wall at the insertion of the hepato-gastro-duodenal ligament and directly penetrate the pancreas, which in this area displays a high density of neurons. This condensation of neurons has been considered a real nervous center. From here the nerve fibers spread to the rest of the gland. The interpretation of Gayet and Guillaumie (29, 30), however, is that the vagi secretory fibers traverse the duodenal wall for different distances. The major part leaves the digestive tract segment to enter the pancreas either at the accessory or the main pancreatic duct. These anatomic pathways are partially supported by the secretory results obtained following electrical stimulation of the pancreatic gland surface. Indeed, judging by the magnitude of "pancreon" secretory response, three regions have the greatest sensitivity. These are, respectively, the duodeno-pancreas areas close to the Wirsung and Santorini ducts, and the juxtapyloric zone. Less sensitive regions are the pancreatic splenic tip and the processus uncinatus. When the sensitive areas (Wirsung, Santorini, juxtapyloric), are electrically stimulated, the excitation that starts from these intrapancreatic centers spreads to the rest of the organ. It is interesting that the EPS response to pancreatic surface stimulation is abolished by atropine pretreatment. These physiologic results are consistent with our macroscopic anatomic findings in human cadavers and dogs (31). Indeed, anatomic dissection displays a density of innervation much greater in the head of the pancreas than in the rest of the gland (6, 7, 31). Further confirmation is afforded by histochemical and biochemical demonstration of greater choline-acetylase activity in the head than in the body-tail segment (23–26, 32) (Fig. 3).

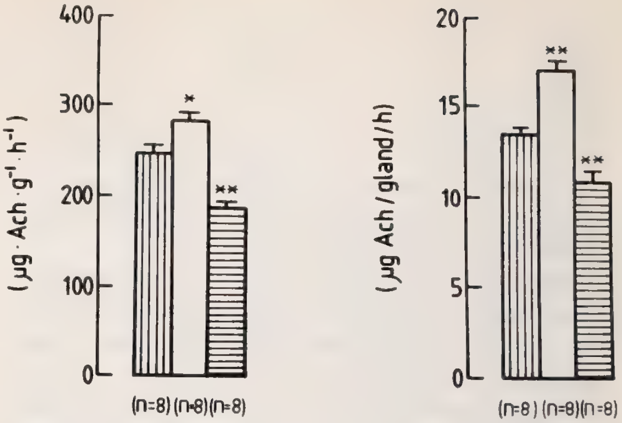

Fig. 3. Choline-acetylase activity (cholinergic tone) is significantly greater in head than in body and tail of pancreatic gland. Left, concentration; right, output. Vertical ruling, total pancreas; white bar, pancreatic head; horizontal ruling, pancreatic body-tail.

The recent findings of Dreiling et al (33) do not support Popielski's concept that the main pathway of vagal pancreatic secretory fibers traverse the pylorus. Indeed, pyloric transection did not alter the basal, the sham-fed, the secretin-CCK and histamine-stimulated pancreatic and gastric secretion. However, a 30%–50% decline of serum PP following pyloric transection suggests that some of the PP cell secretory fibers do pass through the pylorus to the duodenum and innervate the pancreatic head and uncinate process.

In the rat, there is, at present, no precise knowledge of the anatomic pathways of pancreas innervation. In addition to the numerous fibers that traverse the gastric antrum, there are primary cholinergic and peptidergic neurons. All these constitute a complex autonomic nervous brain (AANB). Its influences are exerted not only in the exocrine and endocrine pancreas but on the biliary tract and the gastric fundus (8, 9). From the AANB, the nerve fibers arrive at the pancreas either through the pylorus or bypassing it following the nerves of the lesser curvature and/or the branches that follow the blood vessels of the greater curvature.

As in the gastric antrum, a similar autonomic nervous brain exists in the duodenum (DANB) with primary cholinergic and peptidergic neurons. Electrophysiological stimulation reveals that at the level of the wall of the digestive tract there are pre-ganglionic fibers that go both to the central nervous system and the celiac ganglion where these fibers make synaptic connections with cell neurons. Several observations corroborate these pathways. One is that intraduodenal instillation of hydrochloric acid inhibits gastric contractions (10, 36–38). This response persists after celiac ganglion decentralization and is abolished by celiac ganglionectomy. Ileal distension also inhibits EPS (37). This effect persists after jejunal section and reanastomosis as well as after celiac ganglion decentralization, but is abolished after celiac ganglion exeresis. Dreiling et al have recently confirmed these findings in the dog (39–41). In their investigations, they evaluated the effect of bilateral cervical vagisection as well as alterations of pancreatic duct pressure elicited by the introduction of alcohol into the stomach and duodenum. They found that bilateral vagisection resulted in decrease in pancreatic duct pressure, but what is more convincing is that the infusion of 50 ml of 30% ethanol into the stomach elevates pancreatic duct pressure, whereas the same dose infused into the duodenum triggers depression of duct pressure. Another suggestive finding is that these changes are abolished by prevous cervical vagisection. This clearly indicates that the AANB and DANB are important reflex centers and suggest that the peripheral "brains" may play an important role in the alcohol-evoked EPS changes as well as the histopathology elicited by acute and chronic alcoholism.

At present there are many examples of linkage between different segments of the digestive tract which are independent of the central nervous system but rather involves integrative participation of the prevertebral ganglia. A finding that demonstrates the existence of primary neurons within the wall of the digestive tract is Daniel's observation (38) that one week to one month after thoracic vagal sectioning, a significant number of neuronal fibers had not degenerated in the Latarjet's nerves at the lesser curvature of the stomach. To explain this finding, the cell bodies of these fibers which have escaped degeneration must be present in the digestive tract wall, most probably in the antral stomach and/or in the duodenum.

All the foregoing anatomical considerations elucidate the existence of a cephalic phase in the control of the EPS. Thus, in dogs, sham feeding induces a slight increase of flow (10 to 15%) and of protein (25%) of EPS compared to the augmentation obtained with a test meal (42). A cephalic phase exists also in humans, but comparison with the response to a test meal has not yet been done (43–47). Recent studies have compared the responses to sham-feeding and to a maximal stimulus with secretin plus cerulein. Sham feeding resulted in a close-to-maximal flow rate and ecbolic response but the bicarbonate output was slight, 15% of that observed with maximal secretion. Atropinization decreased protein output but did not significantly depress bicarbonate secretion in this study.

These findings suggest the probable involvement of VIP, which normally induces an atropine-resistant hydelatic secretion. Other studies have compared sham-feeding with a maximal stimulus by CCK-octapeptide. In these experiments, an EPS response was only obtained when sham feeding was superimposed on a secretin perfusion. The sham-feeding protein response was equivalent to 50% of that observed with maximal octapeptide CCK stimulation. Atropine was without effect on these responses. These findings would suggest activation in the central nervous system of one or several peptides with ecbolic stimulation of "pancreon" units. One of the candidates for this effect is bombesin (gastrin-releasing peptide or GRP). This peptide, which can be released from the "intermediate autonomic brains," "antral," "duodenal," and "celiac," and/or the pancreas itself, has an ecbolic capacity that is atropine-resistant. GRP, in fact, has been postulated as a probable mediator of the cephalic phase. This possibility is suggested by the fact that antral acidification or antrectomy is said to abolish the EPS stimulation triggered by sham-feeding. On the other hand, Konturek et al (48) have recently shown, in dogs, that antral mucosectomy does not impair the pancreatic protein secretory increment elicited by sham-feeding, despite the fact that gastrin release is depressed and that PP release is not modified.

In the *gastric phase* of EPS the starting point of the reflex can be the gastric fundus (fundus-pancreatic reflexes). These were identified by Harper and White (49–51). In order to interrupt them completely it is necessary to cut the vagi and the splanchnic (51). The second reflex zone is the stomach antrum (reflexes antrum-pancreatic). Their participation, apparently more important than those arising from the fundus, was shown in dogs (50). Distention of antral pouches with an acid solution with the aim of preventing gastrin release, induces an ecbolic EPS equivalent to 45% of the response obtained by a maximal CCK stimulation. In contrast, the hydrelatic component is much less; being approximately 5% of that observed with a maximal secretin stimulation. In this same animal, it has been shown that the early EPS response elicited by a test meal is dependent primarily on antral reflexes and only secondarily on fundus-pancreatic reflexes (53). These data were obtained by analyzing the EPS results before and after selective antral vagotomy and truncal vagotomy. Moreover, the effect of atropinization was also studied in these protocols. With muscarinic blockade, there were no changes in the rate of flow, but protein response was diminished in 60%. Antral selective vagotomy depressed the protein pancreatic secretion in a proportion similar to atropine (65%), but with the striking difference that the rate of flow was also inhibited (70%). It is remarkable that adding truncal vagotomy to selective antral vagotomy did not influence the degree of EPS depression (53). These responses suggest that the cephalic and fundus-pancreatic reflexes have a relative participation in respect to those that arise from the antrum in the early EPS response that follows an ingested test meal (Fig. 4) (53).

The foregoing results are consistent with the findings of Gayet and Guillaumie (29, 30) when they incised the mesentery of the lesser curvature of the stomach at different levels. The effect of these incisions on the test-meal-induced EPS was almost identical to that obtained with selective antral vagotomy and muscarinic blockade with atropine. This indicates that the early EPS following a test meal results from a reflex originating in antral afferent pathways triggered by gastric distension and changes of intraluminal pH. Indeed, after antral selective vagotomy, intragastric infusion of HCL elicits inhibition of EPS which is abolished by atropine (53). Thus, the involvement of an AANB in the control of EPS is clear, at least in the dog.

Supporting this concept are the findings of Dreiling et al (39–41) that intragastric ethanol resulted in an increase of intrapancreatic duct pressure which could be abolished by cervical vagotomy. Further support is provided by a report disclosing a linkage between the antrum and the endocrine pancreas (PP secretion) (54). This study was performed in animals with and without pyloric transection by stimulating the vagal pathway through hypoglycemia induced by insulin injection. Following section of the pylorus, contrary to what happens when it is left intact, there is a significant decrease in the PP blood levels induced by insulin hypoglycemia. This response is in agreement with Dreiling's finding of a fall of PP blood values following pyloric transection (33).

In the *intestinal phase* of EPS, the arc reflexes start in the duodenum, primarily from its proximal segment, in the region between the pylorus and the papilla of Vater. These reflex arcs were originally proposed by Popielski (27, 28), a member of Pavlov's school. Later Gayet and Guillaumie (29, 30) described the nervous connections between the duodenum and pancreas. Following a period in which these reflexes were disregarded, they were re-recognized by Thomas (27, 28), but their physiological importance was not appreciated until a series of experiments in dogs during the last 15 years, including those performed by Thambugala and Baron (55), Tiscornia et al (56) studying responses to a continuous perfusion of secretin or secretin plus CCK following anesthesia of the papilla of Vater, and a series of tests carried out by Grossman et al (57–66) involving subcutaneous autotransplantation of a segment of canine pancreas (64). The latter studies in canines revealed a delay of the pancreatic enzyme response (amylase) to intraduodenal infusions of aminoacids following atropine (59). Along the same line, a study in humans revealed that hexamethonium totally blocked the pancreatic hydrelatic and ecbolic response, but not the biliary response to the intragastric infusion of milk and dl-methionine (67). These findings were in agreement with the results obtained in Thery-Vella duodenal fistula canines (67) that infusions of HCL, milk, or methionine in the duodenal segment evoke an augmentation of the rate of flow and enzymes of the EPS, a response abolished by an intravenous infusion of hexamethonium. Recently, it has been reported that in humans, activation of receptors of volume and osmolarity in the duodenum excites a similar EPS response which is blocked by atropine (68). A similar reflex arc is involved in the depression of intrapancreatic duct pressure induced by intraduodenal ethanol, a response which is prevented by previous cervical vagisection (39–41).

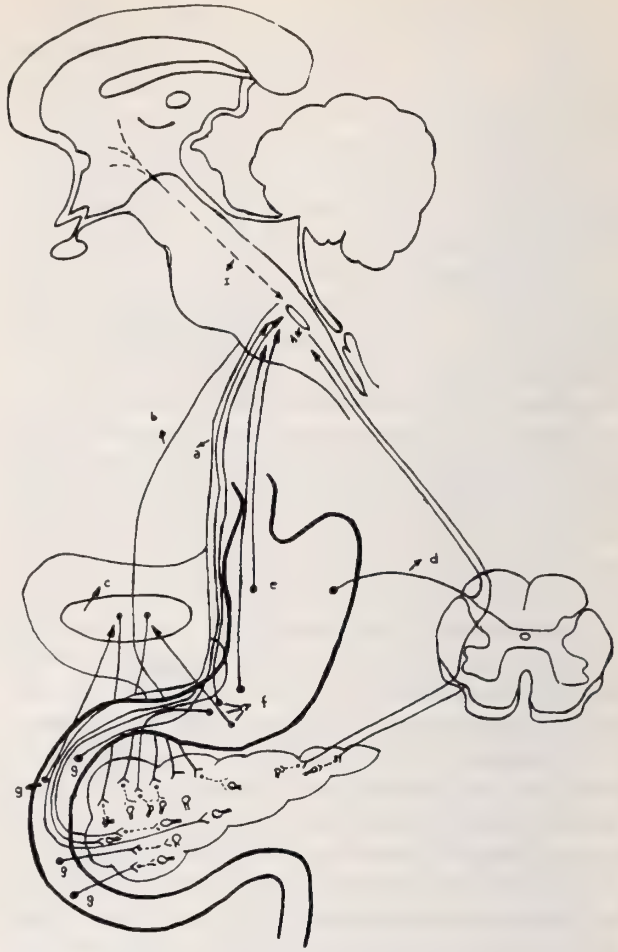

Fig. 4. Pathways of neural reflexes (cephalic, gastric, and intestinal) that normally influence exocrine pancreatic secretion: primary neurons in gastric fundus (e), antrum (f), and duodenum (g). Participation of vagus nerves (a, b), spinal cord and splanchnic nerves, and integrative influence of celiac plexus (c). Vagal cholinergic fibers that pass through celiac ganglion (b) do not make synapse in this structure.

We believe (6, 7, 31, 56) that the anatomic pathways of these duodeno-pancreatic reflexes could be of three different types, short, intermediate, or long. In the short pathway, the impulses originated in the neuronal activity of the parietal plexus are transmitted directly either to the "pancreon" units and/or the intrapancreatic ganglia. The activity of the latter contribute to the intrapancreatic cholinergic tone. In the intermediate pathway, these starting from the same sources as the previous ones are integrated in the celiac ganglion. In the long pathway, these reflexes originating in the digestive tract go to the hypothalamic-bulbar centers from which they return to pancreas level (Fig. 5). The main anatomic pathways, afferent and efferent, are the vagal nerves. It is probable that a percentage of these reflexes could be carried out along the splanchnic nerves, passing through the celiac ganglion. This type of duodenopancreatic reflex activity may be blocked by atropine. The fact that hexamethonium can also block these reflexes (67) from the intestine indicates ganglionic mediation and preferential passage of impulses through nicotinic receptors. These positive cholinergic reflexes exert their influence on the acinar segment of the "pancreon" units (enzymatic secretion), on the centro-acinar-ductal segment (hydrelatic) and on the duct system (intrapancreatic hypertension).

The control of intrapancreatic blood flow (vasodilation) appears to depend on the release of VIP (17, 69, 70), a regulatory peptide released with acetylcholine that modifies the receptors of the target organ, enhancing the efficacy of acetylcholine (71).

Grossman hypothesized that a positive arc reflex from the intestine to pancreas could be initiated paracrinically by CCK. This mechanism, paracrinic-neural, would be triggered when the intensity of the endogenous stimulus is weak for the release of hormones, ie. fat and/or aminoacids in the intestinal lumen. When the intensity of the endogenous stimulus is strong, and the release of CCK from the endocrine cells is high, this peptide would not only excite the afferent nerve fibers paracrinically but also would enter the blood stream and stimulate the "pancreon" units in an endocrine fashion. Similar activity has been postulated for bombesin (72).

Considering all these physiologic data of EPS, the conclusion seems justified that the influences exerted on the pancreas by the DANB are of greater magnitude than those arising from the AANB. Indeed, in humans, the enzymatic pancreatic secretion in response to a liquid test meal containing proteins and fats is not altered by an 80% distal gastrectomy. This occurs despite the fact that this intervention removes the antrum, which results in a marked depression of pepsin and hydrochloric acid release as well as impairs the gastric capacity to emulsify the fats and disperse solid food (73). In contrast, in dogs, extragastric vagotomy (74); or section of the hepatic and celiac branches, depresses the pancreatic enzymatic response to an intraduodenal perfusion of sodium oleate or tryptophane by about 60%. These results imply the interruption of afferences in long entero-pancreatic arc reflexes.

Singer et al (75) confirmed the existence of long enteropancreatic reflexes by studies in canines which showed that truncal vagotomy depresses enzymatic pancreatic secretion in response to an intraduodenal tryptophane infusion, an inhibition augmented by atropinization. This observation suggests that in addition to long arc reflexes mediated through the vagi, there are short arc reflexes between the duodenum and the intrapancreatic ganglia and/or the "pancreon" units.

The results from experiments in dogs and rats, primarily concerned with the physiopathogenic mechanism of chronic alcoholic pancreatitis (8, 9) and the feedback mechanisms that control basal bile-pancreatic secretion (76), indicate that CCK released from the duodenum by paracrine-neural activity elicits two interplaying mechanisms on the "pancreon" units, one excitatory and the other inhibitory. The excitatory mechanism appears to result from the release of acetylcholine and activation of muscarinic receptors on the "pancreon" cells by means of short, medium, and long arc reflexes. Additionally, a cascade of events is elicited by acetylcholine released through the non-nicotinic pathway. Among these are a regulatory peptide with bombesin-like capacity as well as ecbolic-type prostaglandins. The inhibitory mechanism results from CCK activation of several factors and/or peptides, initiated presumably via the same short, medium and long arc reflexes. Pancreatic polypeptide (PP) undoubtedly is involved as are possibly one or all of the following, ie. somatostatin, prostacyclin, enkephalins, substance P, serotonin, adrenocorticotropic hormone (ACTH), and thyrotropin-releasing hormone (TRH) (8, 9).

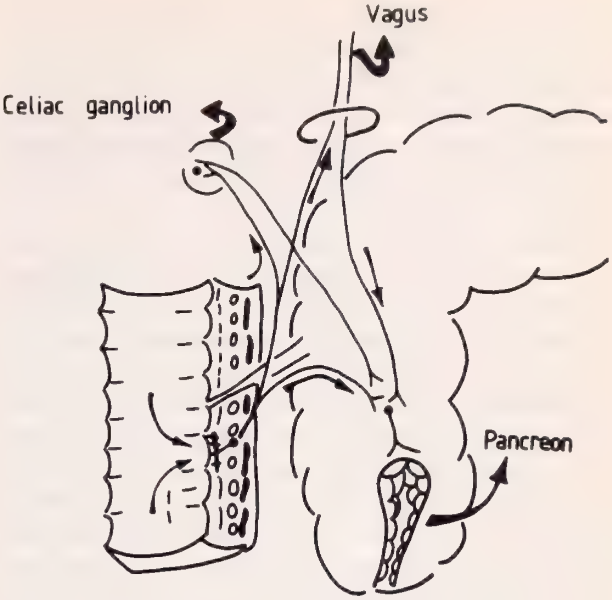

Fig. 5. Pathways of the duodenopancreatic reflexes: short, medium, and long.

In addition to CCK, ethanol, like the scorpion toxin, activates the ganglionic nonnicotinic pathway releasing acetylcholine at nerve endings. This activity is suggested by the following findings: (a) In dogs, Maitrya (8, 9) concluded that alcohol following absorption acted as a gastric secretagogue stimulating the myenteric plexus and the hypothalamic bulbar centers. Both mechanisms are abolished by atropine. (b) Stimulation of gastric pouches with alcohol is potentiated by vagotomy. Note that vagal interruption enhances peripheral neural transmission through the ganglionic non-nicotinic pathways.

(c) In humans, atropine, but not hexamethonium, given either before or after the standard dose of alcohol (20 ml intravenously) almost completely inhibits its gastric stimulatory action. (d) In alcohol-fed dogs, atropine, but not hexamethonium, prevents the excitatory effect of intravenous ethanol on secretin-induced EPS (8, 9).

The intermediate autonomic nervous brains ("antral," "duodenal" and "celiac") are subjected to the modulation of positive and negative impulses coming from the central nervous system (8, 9). During the stage of chronic alcoholism these become hyperactive (8, 9) as a consequence of an ethanol-evoked degeneration of vagal inhibitory fibers. Moreover, alteration of the nicotinic receptors of the peripheral neuron, that is, intermediate autonomic nervous brains and intrapancreatic ganglia, favors nervous transmission through non-nicotinic pathways (6–9). The latter effects are activated by CCK and ethanol with a consequent increase of the intrapancreatic cholinergic tone. We have hypothesized that this change is a pivotal factor leading to the functional and histopathologic changes of alcoholic chronic pancreatitis (8, 9).

Adrenergic. Positive adrenergic impulses in general, like increased sympathetic activity, induce inhibitors of the "pancreon" units. In the rat, however, stimulation of beta-adrenoceptors of the acini increase the enzyme secretion, a response which is blocked by propanolol. Activation of beta receptors in the cholinergic neurons augments the "pancreon" enzymatic response by releasing acetylcholine at postganglionic level (6, 7).

In the rat, contrary to what occurs in dogs, cats, and guinea pigs, sympathomimetic amines, like isoproterenol, adrenaline and noradrenaline, stimulate EPS. Thus, isoproterenol, a beta agonist, increases the hydrelatic component of EPS. Phenoxybenzamine, an alpha-blocker, increases the rate of flow, which is depressed by a beta-blocker. These results suggest the existence of alpha-adrenergic inhibition and of a beta adrenergic stimulation of "pancreon" units (77). In the endocrine pancreas (78, 79), beta agonists primarily enhance somatostatin secretion and to a lesser degree insulin and glucagon release. Alpha adrenergic activation markedly inhibits insulin secretion, slightly depresses somatostatin release, and alleviates glucagon secretion. These findings suggest glucagon to be a stress hormone. Indeed, it is released not only by alpha and beta agonists but also by parasympathetic system activity (78). Moreover, dopaminergic receptors have been described in mouse acinar cells (77, 80, 81). Their activation depolarizes the cell's membranes and results in amylase release. This response is blocked by domperidone. In dog's pancreas, the EPS ecbolic component secretion is also enhanced by dopamine and blocked by domperidone. In humans, however, dopamine lacks this secretory capacity (6, 7). It has been suggested that the role of dopamine, stored in the "pancreon" acinar cells, is topical, discharged into the duct and acting on the centroacinar and ductal cells from the lumen of the excretory system (82). Moreover, Sarles et al (83) have shown that in the mouse dopamine, noradrenaline and isoproterenol excite amylase secretion via mediation of a beta receptor which releases endogenous acetylcholine.

The entire adrenergic system appears to have a trophic effect on the pancreas. In the intestinal epithelium, alpha-agonists have positive action. The beta-agonists, on the contrary, display inhibitory influences. Chemical or surgical sympathectomy, in general, has a depressor activity (84). In the salivary glands, guanethidine-induced sympathectomy evokes depression of mitosis of acinar cells (85). In the pancreas gland, our findings in the rat subjected to interruptions of autonomic nervous system pathways indicates trophic activity of the adrenergic system (23, 26, 34), for example interruption of the afferent limb of the "great trophic circuit" by truncal vagotomy (25, 26) triggers an increase of the weight of the pancreatic gland, particularly of its body-tail segment. This phenomenon is abolished by a concomitant bilateral splanchnicectomy or celiac ganglionectomy. We suggest that interruption of vagal afferent to the central nervous system induces an imbalance within its centers in the hypothalamic-brain stem region, and thereby triggers discharge of trophic impulses which reach the pancreas level passing through the medulla, spinal cord, splanchnic nerves and the celiac ganglion. It would be logical to suppose that trophic discharges could involve the peptidergic system.

Peptidergic. Positive peptidergic impulses originating in the third division of the autonomic nervous system are complex because they comprise a series of peptides from different sources, ie. endocrine cells of the digestive tract mucosa and/or neurons in the gut intraparietal plexuses and pancreatic gland. At present, VIP, bombesin, and CCK-like peptides can exert a positive trophic effect on "pancreon" units.

VIP, regulatory peptide, is present in the whole digestive tract, the vagus nerves, and even somatic peripheral nerves, such as the sciatic. VIP release and activity appear to be coupled with acetylcholine. There is evidence that presynaptic fibers have atropine-sensitive receptors which block VIP release. Vagal stimulation augments VIP blood levels, pancreatic flow, and bicarbonate output, effects which are atropine-resistant and hexamethonium-sensitive.

VIP has a potentiating effect on acetylcholine, increasing the affinity but not the numbers of acetylcholine receptors (71). VIP alters muscarinic receptors to high-affinity conformity and thereby enhances their efficiency in changing Na^+ permeability and secretion. Lundberg et al (71) emphasize that a possible molecular mechanism for the synergistic actions of acetylcholine and VIP is the 10,000-fold increase induced by VIP in the affinity of acetylcholine for muscarinic receptors. These interactions VIP-Ach could help to explain some of our experimental observations with chronic ethanol intoxication. The changes of basal bile-pancreatic secretion induced by pilocarpine, alone or combined with atropine, in controls and alcohol-fed rats, suggest that chronic alcohol intoxication alters the neurons' nicotinic receptors impairing the release of VIP by a cholinergic stimulus, ie. pilocarpine (8, 9). Indeed, the alcohol-induced depression of VIP that we have described in rats could, in part, be responsible for the salivary and pancreatic gland subsensitivity to cholinergic stimulation, a condition that, unexpectedly, is not associated with changes in the number of cholinergic receptors despite the proven elevated intrapancreatic cholinergic tone (86).

Recently, immunohistochemical methods have disclosed the existence of intrapancreatic nerves containing VIP associated with a new peptide, the PHI, that is, N-terminal histidine and C-terminal isoleucine (88). Both peptides are secreted following an electrical stimulation of the vagal nerves, and their pancreatic secretory effects are atropine-resistant and hexamethonium-sensitive (88). This response can be mimicked by cholinergic nicotinic stimulation (88). The PHI-evoked pancreatic flow is 100-fold less than that elicited by VIP (88). Vagal stimulation is always associated with decreased atropine-resistant vascular resistance. VIP and PHI trigger a similar phenomenon. Cosecretion of VIP and PHI is of paramount importance in the neural regulation of the endocrine pancreas and intrapancreatic blood flow (88).

Vagal stimulation by insulin-induced hypoglycemia releases some factor that blocks the secretion of VIP. Indeed, Lygren et al (89), in healthy students, found a significant increase in peripheral plasma VIP when atropine was given together with insulin, whereas insulin or atropine alone had no effect on plasma VIP. Finally, VIP containing nerve fibers whose cell bodies are situated in the myenteric plexi have been detected in the celiac plexus as well as in the pancreas (90, 91).

Bombesin, the gastrin-releasing polypeptide (GRP), is a regulatory peptide present in the digestive tract and the pancreas (72, 92). In the former, the peptide localized in endocrine cells and nerves of the mucosa, submucosa and muscle layers of the gastric antrum and duodenum. In the pancreatic gland, bombesin is found only in neurons. Vagal stimulation increases bombesin blood levels. Its effects on "pancreon" units are primarily ecbolic and secondarily hydrelatic. These secretory actions are not blocked by atropine. Thus, bombesin can be considered a physiologic neurotransmitter in the vagal control of EPS (4). By activation of afferent nerves by paracrine neural mechanism, bombesin can stimulate "pancreon" units by a reflex arc originating in the antral and duodenal autonomic nervous brain. Moreover, bombesin has positive trophic activity on the exocrine and endocrine pancreas. Whether the latter effect is direct or an indirect action resulting from a bombesin-evoked release of trophic agents such as gastrin and CCK is unclear.

CCK-like peptides—"CCK-4-like" (tetrin) and "CCK-8-like"—are peptides resembling or identical with the common C-terminal tetrapeptide amide of gastrin and CCK. These tetrapeptides have been found in most tissues which synthesize gastrin and/or CCK, ie., endocrine cells in the gut in the antrum, duodenum, jejunum, and ileum, neurons in the central nervous system, and nerves of the peripheral nervous system (93). Two regions, the colon and the pancreas, have the highest concentration of these tetrapeptides. In the pancreas, the tetrapeptide-containing nerve terminals are located exclusively around ganglionic nerve cell bodies and around islet cells. The tetrapeptides have the same spectrum of gastrointestinal activities as gastrin-17 and CCK-8 but with significantly lower potencies. They appear to be a major regulator of insulin and glucagon secretion. Pancreatic somatostatin and PP secretion are also influenced by the tetrapeptides, although to a lesser extent. It has been suggested that "tetrin" exerts a local trophic action by neurocine and paracrine release.

CCK-8 accounts for most of immunoreactive CCK in gut neurons. CCK-containing neurons are most commonly found in the colon. Some nerve cell bodies contain both CCK and somatostatin. Neuronal CCK is liberated in the gut by afferent vagal fibers. Thus, ligature of the cervical or thoracic vagus in dog or cat results in a marked accumulation of immunoreactive CCK on the cranial side. This accumulation persists after section of the vagus above the nodose ganglion which induces degeneration of efferent fibers; therefore CCK liberation can be localized to afferent fibers with cell bodies in the nodose ganglion.

CCK receptors have been demonstrated along the vagus nerves in the rat (94). These are subjected, like other neurotransmitters such as opiods, to peripheral transport along the nerve (94). Other neuropeptides, such as somatostatine, substance P, and VIP, have also been detected in the vagi. All can be shown to traverse the cell body in the nodose ganglion to the periphery. It is probable that neuronal CCK, as well as bombesin, participates in the pancreatic exbolic response to sham-feeding in humans. This could explain the recent finding that EPS, triggered by sham-feeding, is atropine-resistant (43, 44).

Negative Impulses

The negative component is distinguished by negative cholinergic, adrenergic, and peptidergic impulses.

Cholinergic. Negative cholinergic impulses depress intrapancreatic cholinergic tone. They probably participate in the three phases of the "pancreon" control. Negative cholinergic impulses are primarily mediated by pancreatic polypeptide (PP) and actively affect the peptidergic system.

Adrenergic. Negative adrenergic impulses have an inhibitory influence upon the EPS. Their influences are exerted at different sites. One effect is depression of the firing of central (hypothalamic-brain-stem) and peripheral (intrapancreatic ganglia) cholinergic neurons by means of activation of alpha-2-adrenoceptors (95–98). Another mechanism is blockade of cholinergic transmission by activation of presynaptic alpha-1-adrenoceptors. The consequence is depression of acetylcholine release at postganglionic terminals (6, 7, 12, 98). The inhibitory effect on the "pancreon" is, in part, also due to reduction of intrapancreatic blood flow, a result of activation of alpha-1-adrenoceptors on visceral blood vessels. Furthermore, a new regulatory peptide, neuropeptide Y (NPY), has been identified throughout the peripheral autonomic nervous system, particularly in association with adrenergic nerves (99). Intraarterial infusion of this peptide induces vascular constriction, resistant to alpha adrenergic blockage. Splanchnic nerve stimulation evokes release of NPY in plasma. Hexamethonium pretreatment abolishes this release. After surgical sympathectomy NPY fibers are no longer detectable (99).

The inhibitory effect of the sympathetic nervous system is independent of vasoconstriction and results from action on adrenoceptors of the acinar cells (96, 97). This adrenergic inhibition of EPS appears to have physiologic significance as suggested by the following data (12): (a) Section of the splanchnic nerves increases EPS. (b) Stimulation of the afferents splanchnic fibers, or the infusion of catecholamines, induces vascular constriction and inhibition of EPS. The latter persists even after vascular constriction is abolished by alpha-adrenoceptive blockers such as phenoxybenzamine. (c) Adrenergic stimulation releases pancreotone (100) from the lower segments of the intestinal tract—ileum and colon. Pancreotone is an inhibitor of the "pancreon" units. This physiologic setting would be equivalent and contrary to that resulting from vagal release of gastrin from the stomach antrum. (d) Excitation of the central end of the splanchnic nerves that carry afferent fibers from the ileum induces reflex depression of EPS. A similar effect occurs when the central end of the lumbar colonic nerves, carrying colonic afferent fibers, are electrically stimulated (12).

It has been suggested that at night, and during diurnal interdigestive periods, the exocrine pancreas is under tonic inhibitory control from the upper and lower segment of the digestive tract (12). The factor evoking this tonic inhibition could be the cessation of water and solute transport at the lower end of the ileum and, in some species, the colon. Pancreotone has been suggested as the inhibitory hormone involved. The nervous reflex pathway includes visceral afferent fibers from the splanchnic nerves of the lower end of the ileum as well as the lumbar splanchnic nerves from the colon. Afferent inhibitory impulses pass up the spinal cord to the integrating centers in the brain stem, from which all efferent nervous pathways to the pancreas originate. The inhibition of EPS is effected by efferent sympathetic fibers in the splanchnic nerves supplying the glandular tissue of the pancreas (12).

Nervous inhibitory influences on the pancreas originating from the upper segment of the digestive tract result from negative cholinergic reflexes via PP and inhibitory regulatory peptides, i.e., somatostatin, enkephalins, and substance P. Finally, the anti-CCK factor of Caroli (101, 102) must be considered. This controversial "hormone candidate" is secreted by the gallbladder, possibly the cystic duct wall, and induces active inhibition of gallbladder emptying. The fall of anti-CCK factor in the blood after a fat meal would trigger gallbladder contraction. A physiologic effect on "pancreon" units cannot be excluded.

Tonic inhibition of EPS during the interdigestive period is overridden by a second phase of stimulation of EPS. This occurs 11 hours after ingestion of a test meal and is attributed to duodenal acidification (103).

Other inhibitory reflexes to the pancreas can be evoked by hypertonic glucose and saline solutions infused in the cat's ileum and colon (104). The origin of these reflexes are osmo- and chemoreceptors in the gut wall. A neural inhibitory reflex of EPS bile secretion is also observed in humans following right colonic infusions of oleic acid, aminoacids and glucose (105).

Further support to the concept of inhibitory cholinergic reflexes from the intestines to the pancreas is provided by the effects reported following distension of the jejunum on pancreatic secretion in the dog (106). Inhibition of pancreatic secretion was observed—a phenomenon which is blocked by previous atropinization or by topical application of 2% lidocaine to the jejunal mucosa.

Peptidergic. Peptidergic negative impulses are elicited by somatostatin, the enkephalins, substance P, and pancreatic polypeptide.

Somatostatin (SOM) originally isolated from the hypothalamus, is secreted by endocrine cells in the gut and pancreas (79, 107–109) by adrenergic neurons, an example of co-storing of a biogenic amine and a regulatory peptide, and in neurons and nerve fibers in the intestinal tract and pancreas. The SOM endocrine cells of the gut and pancreas differ from the classical endocrine cells in possessing protoplasmatic extension that ends in bulbar expansions on the effector cells. SOM has two molecular variants, SOM-14 and SOM-28. Neural and endocrine factors, such as acetylcholine, noradrenaline, prostaglandins, and histamine, are involved in its release. The infusion of acetylcholine excites its secretion from the gastric antrum, fundus and pancreas (110). Concerning interactions between the cholinergic system and the release of pancreatic somatostatin, the results are contradictory. Both enhancement (110) and inhibition (111) have been reported. In fact release of acetylcholine from nerve terminals is blocked by SOM. This raises the possibility of a feedback interplay between cholinergic neurons and SOM. Noradrenaline and dopamine stimulates the release of SOM by activation of a beta-adrenoceptor in the stomach and pancreas. Conversely, SOM inhibits the release of noradrenaline. Another modulating agent of antral and pancreatic SOM is histamine. Tests performed with histamine H_2 blockers (cimetidine) disclose a fall of postprandial SOM secretion. Moreover met-enkephaline, co-stored with gastrin in the G cells of the gastric antrum, depress the release of gastric SOM. Finally, beta-endorphins inhibit pancreatic SOM secretion, a phenomenon abolished by naloxone (109, 110). Thus, SOM is a peptide that block practically all the mechanisms of hormone stimulation of the "pancreon" units (108–111).

Enkephalin-like and endorphin-like activity are detected (112) in the pancreas, in the D cells of the Langerhans' islets, and in the secretory granules of the A cells (4, 112–119). Numerous enkephalinergic fibers have been described in the vicinity of the intrapancreatic ganglia, the pancreatic capsule and the interlobular connective tissue. In the rest of the gastrointestinal tract, enkephalins are detected in the distal segment of the stomach and in the upper jejunum. Their sources are endocrine cells of the APUD series and nerve fibers of the myenteric plexus and the vagus nerves. The endogenous enkephaline appears to brake the pancreatic secretory response. Thus, the EPS of the "pancreon" cephalic and intestinal phases never achieve the maximal secretory capacity obtained with hormonal exogenous stimulation (114). Endogenous enkephalins inhibit the hydrelatic and ecbolic EPS in the dog (114, 116). The endocrine cells that release secretin and CCK have opioid receptors. Their activation inhibit the hormone's release. Both "pancreon" segments, acinar and centroacinar-ductal, also have opioid receptors which upon activation block the respective enzymatic and hydrelatic responses (113). In the small bowel, opioid peptides dilate arterioles and precapillaries and, thus, enhance blood flow and uptake of oxygen (118). Moreover, enkephalins inhibit the mechanical activity and the release of acetylcholine by CCK (118) in the small bowel. These activities, as well as inhibition of EPS, can be linked to depression of intrapancreatic cholinergic tone that normally presents the milieu upon which gastrointestinal hormones—secretin and CCK—act on the "pancreon" units. Ethanol has been reported to enhance beta-endorphins plasma levels (119). In fact, both intravenous ethanol in nonalcoholic dogs (120), and exogenous administration of enkephalin, increase gastric secretion and inhibit EPS (114, 115).

Interesting interactions between CCK and enkephalins are displayed, presumably resulting from striking structural similarities (121). Indeed, CCK administration electively interferes with opioid-induced analgesia. A CCK antagonist, proglumide (121), potentiates and reverses tolerance to the analgesia induced by morphine and endogenous opioids. Presumably, the administration of CCK antagonists could diminish the dose of narcotics necessary to alleviate pain and enhance the antalgic effects of therapeutical procedures like acupuncture (121). In fact, acupuncture releases endogenous opioids in the skin. It has been suggested that chronic administration of opioids may induce a compensatory increase of CCK analgesia (121). This sequence of events may clarify the mechanism of action by which oral pancreatic enzymes alleviate the abdominal pain of chronic pancreatitis. Intraluminal pancreatic enzymes have the capacity, as acupuncture, to release endogenous enkephalins at the level of the duodeno-pancreas. This effect is potentiated by a simultaneous depression of CCK secretion into the duodenum due to a negative feedback mechanism exerted by intraluminal trypsin and chymotrypsin (122–124).

Substance P (SP), the first "brain-gut" peptide discovered, has a dual localization in the gastrointestinal tract. It is present in endocrine cells, together with serotonin, in ganglionated nerve plexuses, and in cell bodies and nerve fibers in the myenteric and submucosal plexus. The source of these SP-containing fibers as shown by denervation experiments, is predominantly intrinsic, but SP is also present in the vagus from which it can be released by electrical stimulation. Sympathetic abdominal ganglia also contain abundant SP-immunoreactivity due to sensory fibers from the gut traversing the ganglia on the way to the spinal cord (4, 108, 124–127). In the pancreas, the presence of SP was demonstrated in septal nerve fibers and pancreatic ganglia suggesting that SP-ergic nerves may innervate acinar and/or endocrine cells. The distribution of SP in primary sensory afferents affords circumstantial evidence that SP is involved in peripheral nociception. SP is also present in the descending serotoninergic raphespinal pathways which mediate supraspinal anesthesia.

In dogs, SP infused intravenously inhibits pancreatic bicarbonate and protein secretions induced by secretin, cerulein, feeding or duodenal acidification. SP also inhibits the choleresis evoked by CCK or VIP. SP at low doses induces analgesia by releasing opiates, whereas at high doses SP's direct excitatory effect on nociceptive neurons causes a hyperalgesia negating the analgesic effect of released opiates.

Whether SP is released from free nerve endings during antidromic vasodilation by the axon reflex is still debated. Since SP is one of the most potent histamine-releasers in the human skin, SP release from nerve endings could be a factor in the pathophysiology of itch, which is mediated by the same unmyelinated fibers as pain (127).

Longo and Sosa Gallards have speculated that SP could be the peptide involved in acute biliary pancreatitis. They postulate that an antidromic reflex triggered from the interstitium of the pancreatic gland plays a pivotal role (128).

Finally, SP has been observed to elicit permeability changes of the vascular system to serum albumin in the small bowel. Such an action in the pancreas has not yet been confirmed (129).

Pancreatic polypeptide (PP) is an important negative component in the neuroendocrine control of exocrine pancreatic secretion. PP endocrine cells are located in the ductal epithelium and in the Langerhans islets, primarily in the pancreatic head. Release of PP is cholinergic dependent and atropine-sensitive (130–141). Denervation of the gastric antrum depresses PP release. Selective but not parietal vagotomy impairs PP secretion. These data confirm neural interaction between the stomach and the head of the pancreas.

PP release (Fig. 6) is elicited by digestive hormones (141) such as CCK, secretin, and bombesin, but PP is fundamentally an anti-secretin and anti-CCK agent, acting in accord with the classical vagal inhibitory fibers described by Pavlov. We have noted that transection of the vagus in the neck results in degeneration of these fibers.

Possible trophic action of PP on the pancreas remains to be elucidated. Suggestive findings include the fact that the fall in the pancreatic wet weight observed at autopsy of the diabetics spares the head of the organ, precisely where concentration of this peptide is higher (141). The PP concentration in the blood rises with ad-

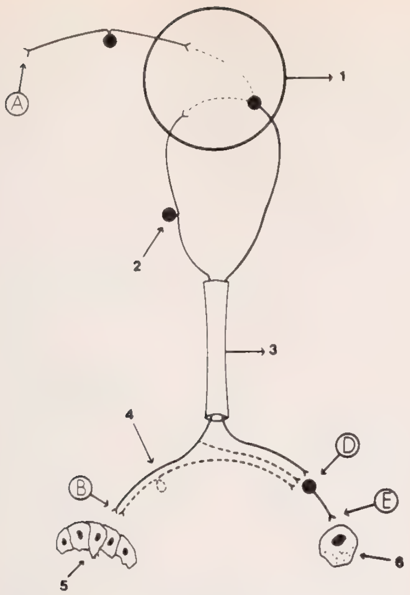

Fig. 6. During sham feeding, afferents through cranial nerves (A) are received in central nervous system (1). PP cell (6) is influenced by vagal efferent impulses (3). In gastric and intestinal phases (5) of exocrine pancreatic secretion, PP cell is probably influenced by vagal reflex (4), long or short (dotted line). Regulatory peptides, such as bombesin, CCK, activate reflex in (B) and perhaps also affect postganglionic neuron (D). It has been postulated that CCK, VIP, secretin could also act on (E), although most probable locus of action is (B) or (D). *Adapted from Schwartz (ref. 141).*

vancing age, but what this means functionally has not been clarified, nor are the relationships between PP blood levels and ingested foodstuffs clear. The findings are discordant. Thus, ingested proteins are the most powerful releasers of PP. However, intravenous infusions of aminoacids such as arginine, leucine or alanine, do not alter the PP blood levels. A similar phenomenon is observed following infusion of triglycerides. On the other hand, both intraluminal and parenteral glucose have a suppressor effect (141).

The cephalic and gastric signals to the PP cell after a test meal are vagally mediated. After truncal vagotomy, the signals elicited by nutrients in the gastrointestinal tract are still able to evoke PP release. Therefore, direct nervous connections between the gastrointestinal tract and the PP pancreatic endocrine cells (141) (Fig. 6) must exist.

Synthesis of the Pancreatic Peptidergic Innervation. In fetal pigs and humans, endocrine cells appear earlier than nerves. In humans, endocrine cells are observed first in the gastric antrum, duodenum and pancreas, and later in the distal bowel (142). VIP and enkephalin peptidergic nerves are first seen at the 15th and 16th week of gestation; SP and NPY nerves appear at a later stage (142).

In the adult pancreas the main hormones of peptidergic innervation are VIP, generally costored with PHI, "tetrin," SP, ENK, NPY. These have been detected innervating the "pancreon" units, Langerhans' islets, and intrapancreatic ganglia. The Vipergic nerves innervate the acini and the blood vessels. Vagal excitation releases VIP and PHI from the splanchnic area (88) as well as from intrapancreatic nerves, releases coinciding with an atropine-resistant secretion of water and bicarbonate and a concomitant drop of the vascular resistance. Stimulation of the splanchnic nerves enhances NPY secretion (99), inducing vasoconstriction resistant to alpha-adrenoceptive blockade. Hexamethonium pretreatment prevents the rise in blood level enhancement. Following sympathectomy, NPY perivascular fibers can no longer be detected (99).

In vitro studies disclose that the pancreatic acinar cells possess receptors for at least four kinds of peptides: CCK/gastrin, bombesin, SP, and secretin/VIP. Insulin has no effect but does potentiate enzymatic secretion induced by CCK and acetylcholine. Secretin and VIP also potentiate the effect of other peptides and of cholinergic agonists on enzymatic secretion (143).

The peptides with a primary effect on the bicarbonate secretion are secretin and VIP. In rats, dogs, and humans, VIP is a partial agonist, but in cats and pigs a complete agonist. Bicarbonate secretion in response to secretin is potentiated by peptides of the CCK/gastrin family. CCK, bombesin, and gastrin stimulate enzymatic secretion but also affect the rate of flow and bicarbonate, especially in the rat. Secretin can also stimulate enzymatic secretion. We have shown this activity in dogs (144, 145), a finding confirmed in humans (146).

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Protease-Antiprotease Balance in Serum And Pancreatic Tissue in Acute Experimental Pancreatitis in Rats

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Abstract

After inducing experimental acute pancreatitis in rats, we measured trypsin, trypsinogen, alpha$_1$-antitrypsin, alpha$_2$-macroglobulin, and antithrombin-III activity in pancreatic tissue. In the third hour of the experiment, a twofold increase in antithrombin-III and consumption of alpha$_2$-macroglobulin was found. After six hours, alpha$_1$-antitrypsin was elevated. At 12 hours into the experiment, increases in trypsin and trypsinogen were noted, followed by progressive decreases. Morphologic study showed an increase in number of zymogen granules in pancreatic tissue, which closely corresponds to the biochemical findings. We conclude that acute experimental pancreatitis is caused by disturbance of the protease-antiprotease balance.

Despite many investigations, the pathogenesis of acute pancreatitis remains to be solved. This problem is important not only from a theoretical point of view but also with respect to clinical procedure. Among the many theories that have been offered is that increased proteolysis is predominantly responsible (1–6). This attractive idea was questioned by Beck et al (7, 8), who found no decrease in trypsinogen activity in pancreatic tissue during acute experimental pancreatitis.

Therefore, it seemed reasonable to determine the content of trypsin and trypsinogen in the pancreatic tissue at different times after induction of acute pancreatitis under standard conditions. For a complete evaluation of proteolysis, it was necessary to measure the main proteolytic inhibitors, both in serum and in pancreatic tissue.

Materials and Methods. Acute experimental pancreatitis was induced in male Wistar rats (mean weight 375g ± 27) by retrograde injection of 5% sodium taurocholate into the bile duct ligated at the liver chyli.

The animals were divided up into the seven groups: group I, healthy rats; Groups II–VII, rats killed at 3, 6, 12, 18, 24, 48 hours respectively after induction of pancreatitis.

Rats were deprived of food but not of water for 24 hours before the operation. Anesthesia was induced with an intraperitoneal injection of Urethan (Xenon, Lódź, Poland).

Trypsinogen, trypsin, and chymotrypsin in homogenized pancreatic tissue and serum were measured by Erlanger and Nagel colorimetric methods, using Boehringer Mannheim GmbH kits. The trypsinogen was activated with 0.2% solution of enterokinase (E-1256 Sigma Co., St. Louis, Missouri). Protein concentration was measured according to the Lowry method (9). The concentration of proteinase inhibitors alpha$_1$-antitrypsin, alpha$_2$-macroglobulin, and antithrombin III was measured using radial immu-

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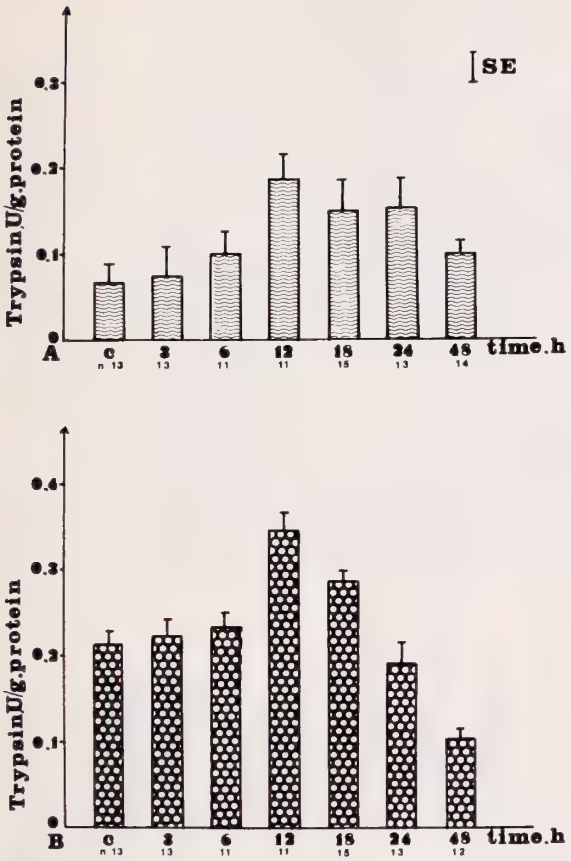


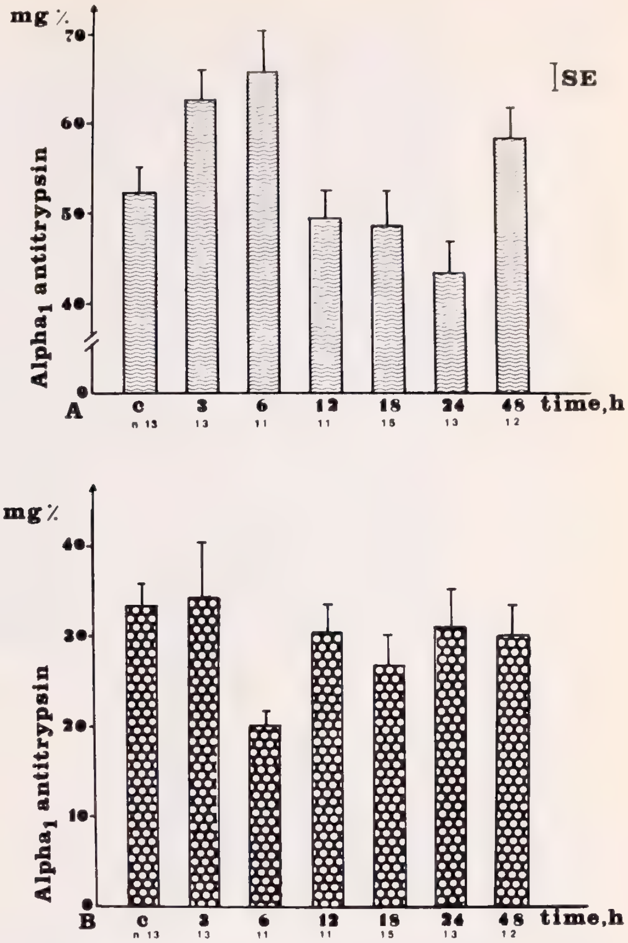


Fig. 1. Left Trypsin (A) and trypsinogen (B) activity in pancreatic tissue in the course of acute experimental pancreatitis. **Fig. 2. Right** Concentration of alpha$_1$-antitrypsin in serum (A) and in pancreatic tissue (B).

nodiffusion partigen plates by the Mancini method (10). Ultrastructural changes in the pancreas were examined with the TESLA BS-613 electron microscope.

Results. During the first 6 hours of acute experimental pancreatitis, almost no changes in tissue pancreatic trypsin and trypsinogen were evident (Fig. 1). But at 12 hrs into the experiment, levels distinctly increased, then decreased.

Antithrombin-III concentration increased twofold at the third hour of the experiment, in both serum and pancreatic tissue. This enormous concentration of antithrombin-III lasted only 12 hours. After this time levels decreased dramatically, falling even lower than initial values (Fig. 2).

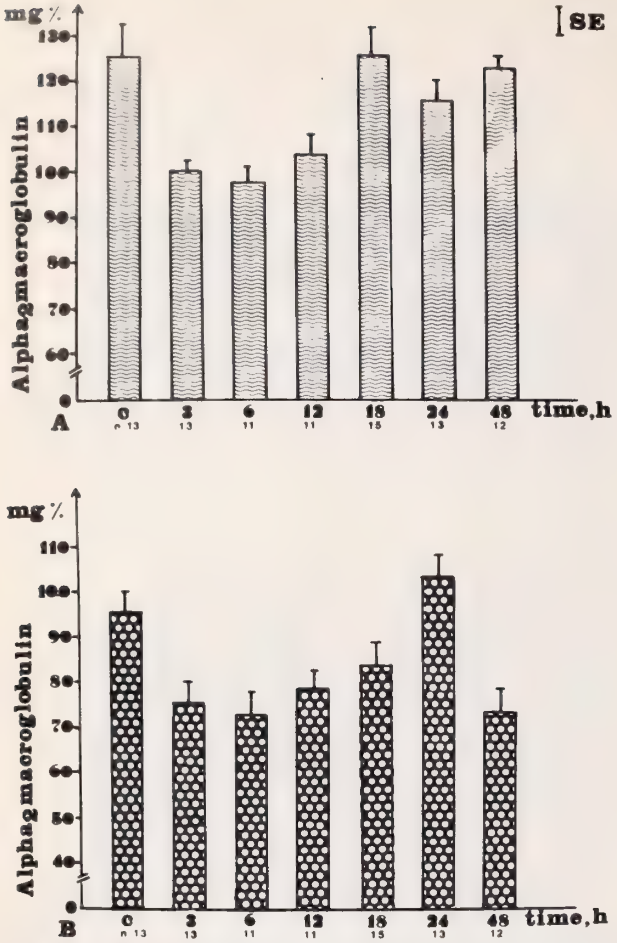
Evident consumption of alpha$_2$-macroglobulin in serum began at the third hour. In serum tested at 18 hr, the concentrations of this inhibitor were close to control levels. In pancreatic tissue, total recovery to control values was reached after one day (Fig. 3).

A transitory elevation of alpha$_1$-antitrypsin concentration in serum occurred 6 hr into the experiment, followed by decrease in the next 18 hr. In pancreatic tissue, no significant variations of this factor were noted (Fig. 4).

Electron-microscope findings were in good agreement with the biochemical results. Numerous zymogen granules were seen in pancreatic tissue after 12 hours of acute pancreatitis. In the same time span the highest value of tissue trypsinogen was found (Fig. 1).

Discussion. The most important changes in the first 6 hours of the experiment were increased antithrombin-III both in serum and in tissue, elevation of alpha$_1$-antitrypsin, and remarkable decrease of alpha$_2$-macroglobulin in serum and in tissue.

In the second period of our observations, a dramatic decrease in serum antithrombin-III and serum alpha$_1$-antitrypsin was observed. In this period the alpha$_2$-macroglobulin returned to starting values. At 12 hours the tissue trypsin-



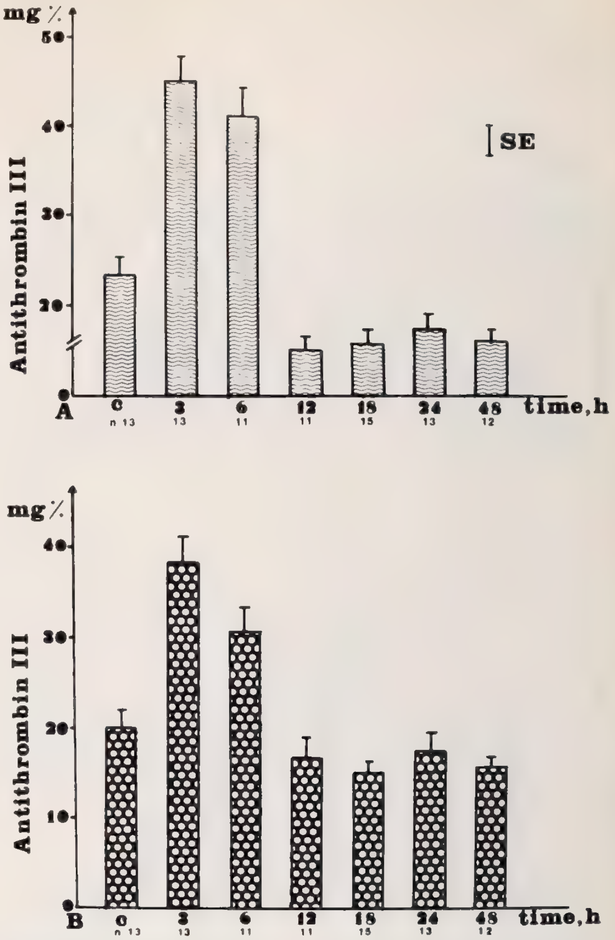


Fig. 3. **Left** Concentration of alpha$_2$-macroglobulin in serum (A) and in pancreatic tissue (B). Fig. 4. **Right** Concentration of antithrombin-III in serum (A) and in pancreatic tissue (B).

ogen activity reached its highest value, and this reading was supported by electron microscope findings.

The literature points to the hemostatic disorders in the pathogenesis of acute experimental pancreatitis. In the early period of this disease, hypercoagulability has been found to be a dominant factor. In the second phase of acute pancreatitis, hypocoagulability has been noted.

On the other hand, it is known that antithrombin-III is the main inhibitor of coagulation. The appearance of high activity of antithrombin-III in the first period of acute experimental pancreatitis may be seen as a factor protecting against multiactivating enzymatic agents such as trypsin. This enzyme is accepted as a trigger mechanism for the initiation of enzymatic cascade pathway, including hemostatic disorders. A supporting role in this protective reaction may be played by the increase of serum alpha$_1$-antitrypsin. One can therefore suggest that these two inhibitors play an important role in the development of acute experimental pancreatitis.

Adham et al (11) describe the existence of a serum protease-antiprotease balance that can be disturbed in acute pancreatitis. They found a decrease in the antiprotease capacity of serum in this disease. Our data are in good accord with these observations.

We underline that our biochemical finding of an increase in pancreatic trypsinogen is supported by the increase in number of zymogen granules and especially the appearance of immature forms.

However, in the literature, there are differing opinions on the role of protease and its inhibitors as pathogenetic factors in acute pancreatitis. Goldstein et al (12), Imrie et al (13), and Mero et al (14) describe intensification of serum antitrypsin activity, whereas Rao et al (15) have found a decrease in this activity.

The tendency of serum alpha$_2$-macroglobulin to decrease in acute pancreatitis in humans was described by Imrie et al (13) and McMahon (16); other authors have not found any changes in this inhibitor in the course of this disease (11, 12).

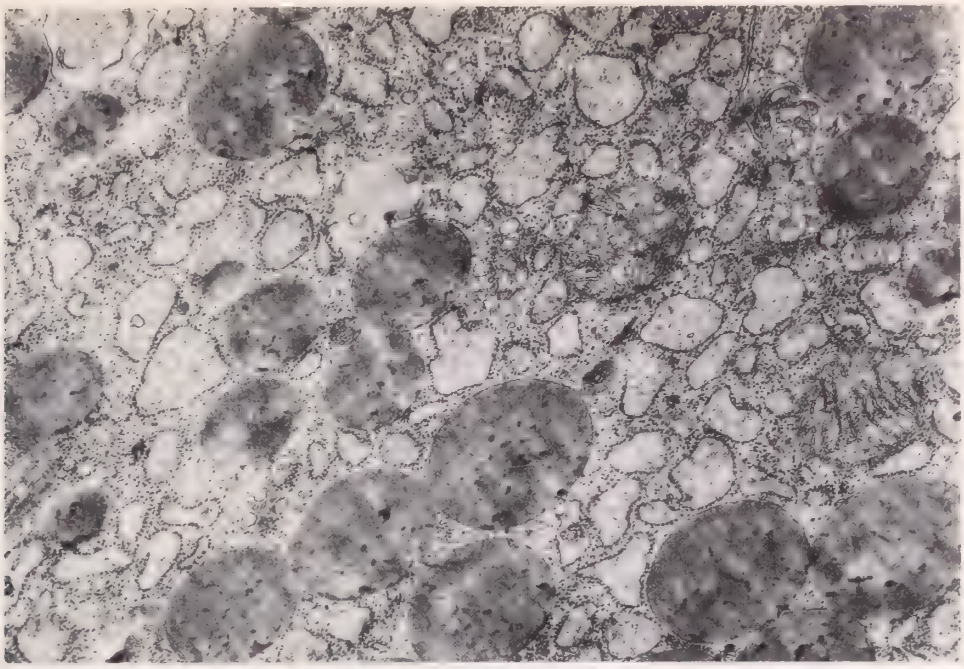


Fig. 5. Portion of acinar pancreatic cell. Some zymogenic granules and dilated cisternas of rough endoplasmic reticulum are seen (original magnification 9900 ×).

The role of proteolytic inhibitors in acute pancreatitis also remains controversial.

In summary: we stress that the changes in protease-antiprotease balance may play a decisive role in the development of acute pancreatitis. The leading cause of differences of opinion among the many investigators may depend on the phase of the disease at which testing was done.

These observations have a special impor-

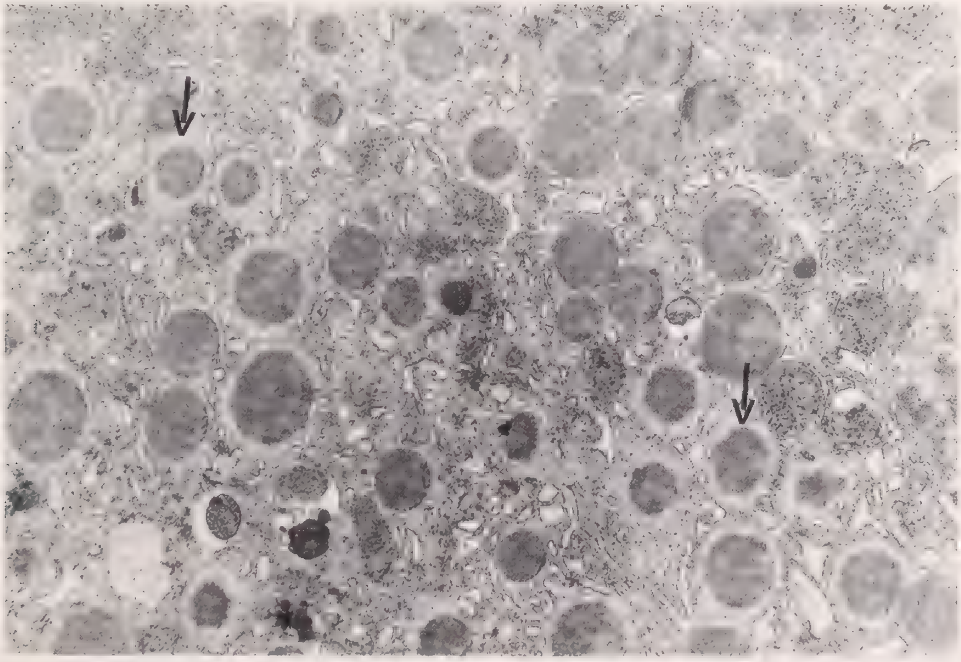


Fig. 6. Numerous conspicuous zymogenic granules of different size and electron density in cytoplasm of acinar pancreatic cell. Some could correspond to premature zymogenic granules (arrows) (original magnification 4750 ×).

tance in clinical practice, when we never know what stage the disease is in.

Further investigation is called for.

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Experimental Duodenectomy in Dogs Preserving the Sphincter of Oddi and the Outlets of the Pancreatic Ducts

GEORGE TOUBANAKIS, M.D., DIONYSIA EUSTATHIOU, M.D., AND ANDREAS POLYDOROU, M.D.

Abstract

We carried out an experimental study in seven dogs of duodenectomy preserving the sphincter of Oddi. The removal of the duodenum preserved the area which contains the sphincter of Oddi and the outlets of the pancreatic ducts, together with a small section peripheral to the pylorus. To this segment the first loop of the jejunum was anastomosed end to end. The preserved area of duodenum was sutured to the opening of this loop. Postoperatively, function of the sphincter of Oddi, the biliary system, and the liver and pancreas were not affected. The similarity of anatomy and physiology of the intestinal and bile system in humans and dogs creates well-grounded hope that this method can be applied successfully in extensive human injuries and benign tumors of the duodenum or the pancreas, in patients whose surgical management requires duodenectomy.

Duodenectomy is indicated for surgical management of some cases of extended injuries or benign tumors of the duodenum or the pancreas. During duodenectomy the area containing the sphincter of Oddi as well as the outlets of the pancreatic ducts is also removed, although this area may not exhibit any changes (1–6).

This is done not because the significance of the preservation of this area has not been established, but because the issue of preservation of the area containing the sphincter of Oddi and the outlets of the pancreatic ducts, following duodenal removal, has not been investigated.

The present experimental study was undertaken in an effort to investigate the results of preserving the area containing the sphincter of Oddi and the outlets of the pancreatic ducts following duodenectomy sutured in dissection made in the antimesenteric side of the first loop of the jejunum.

Materials and Methods. The experiments were carried out in dogs because of the similarity of the canine and human intestinal and biliary system (7). Seven experimental animals weighing 10–12 kg, aged 1–3 years, comprised the material of the present study. Nembutal, 16–20 mg/kg, was given intravenously for anesthesia. The technique was as follows (Fig. 1):

1. A midline incision was made in the peritoneal cavity.

2. A longitudinal incision in the duodenum was made and determination of the area containing the sphincter of Oddi was carried out by the ejection of bile into the duodenum, by means of compression of the gallbladder.

Separation of the duodenum from the adjacent tissues was carried out. Separation began 1.5–2 cm peripheral to the pylorus, was interrupted 2 cm before the outlet of the bile duct, and began again 4–5 cm peripheral to this outlet. This was done in order to include in the segment of the duodenum (which was not separated from the adjacent tissues) the outlet of the bile duct and the minor pancreatic duct, together with the outlet of the major pancreatic duct. In dogs the outlet of the bile duct and the minor pancreatic

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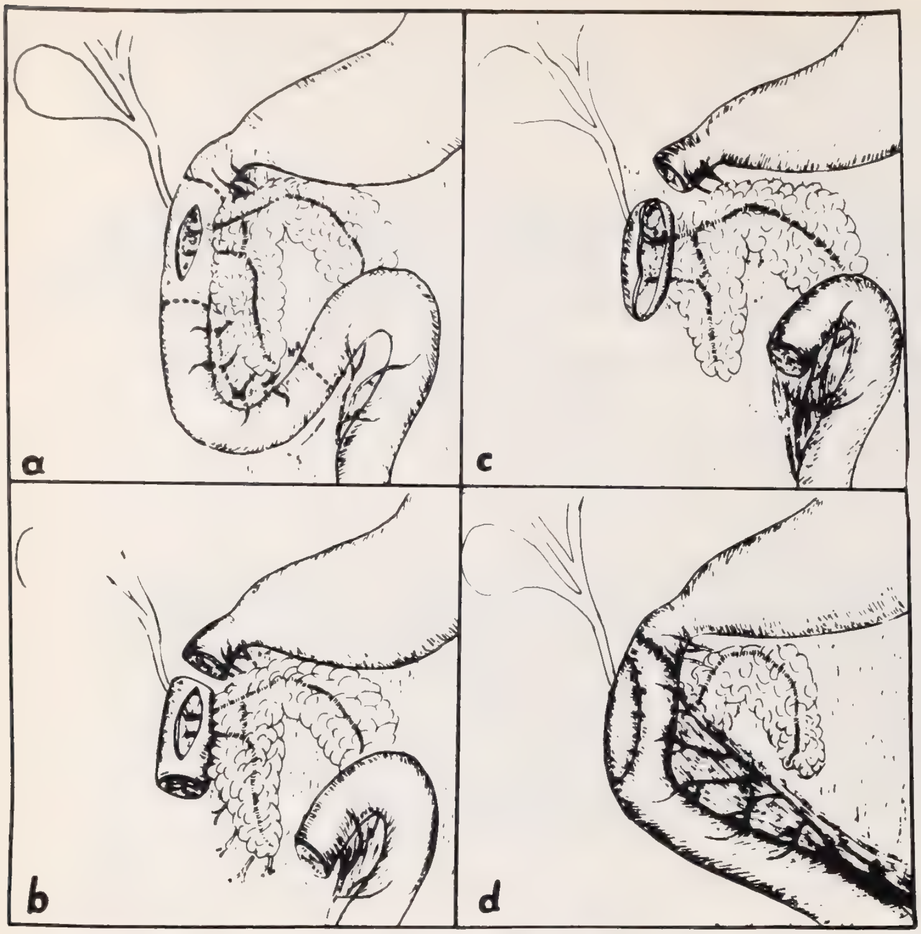
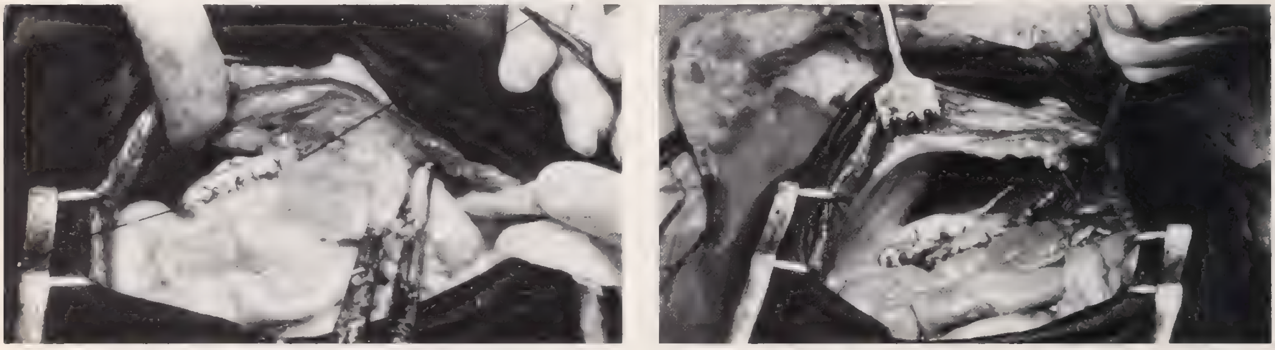


Fig. 1. Left Technique for experimental duodenectomy.

Fig. 2. Terminal operative stage. **Below left** Preserved segment of duodenum sutured in dissection created at initial segment of jejunum and duodenojejunostomy being prepared; Clamps show stump of duodenum and jejunum, which are about to be anastomosed. **Below right** Duodenojejunostomy completed.



duct are together in the area of the sphincter of Oddi and the outlet of the major pancreatic duct is about 3 cm peripheral to the sphincter of Oddi (7). During separation of the duodenum the pancreatic vessels are not ligated, except for their branches which vascularize the duodenal segment that has been separated (Fig. 1a).

4. The segment of the duodenum which was separated is removed (Fig. 1b).

5. The anterior area of the duodenal segment (which remained) is removed and its posterior area, containing the outlets of the bile duct and pancreatic ducts, is preserved (Fig. 1c).

6. Suturing of the preserved segment of the duodenum in an opening created at the antimesenteric margin of the initial segment of the jejunum was done. This opening was made 3–4 cm peripheral to the stump of the initial segment of the jejunum, which was created after duodenectomy (Fig. 1c).

7. An end-to-end anatomosis of the stump of the initial segment of jejunum with the stump of the duodenum, which remained peripheral to the pylorus (Figs. 1d, 2) was performed.

8. Finally, the walls were sutured.

In the first three postoperative days the ex-

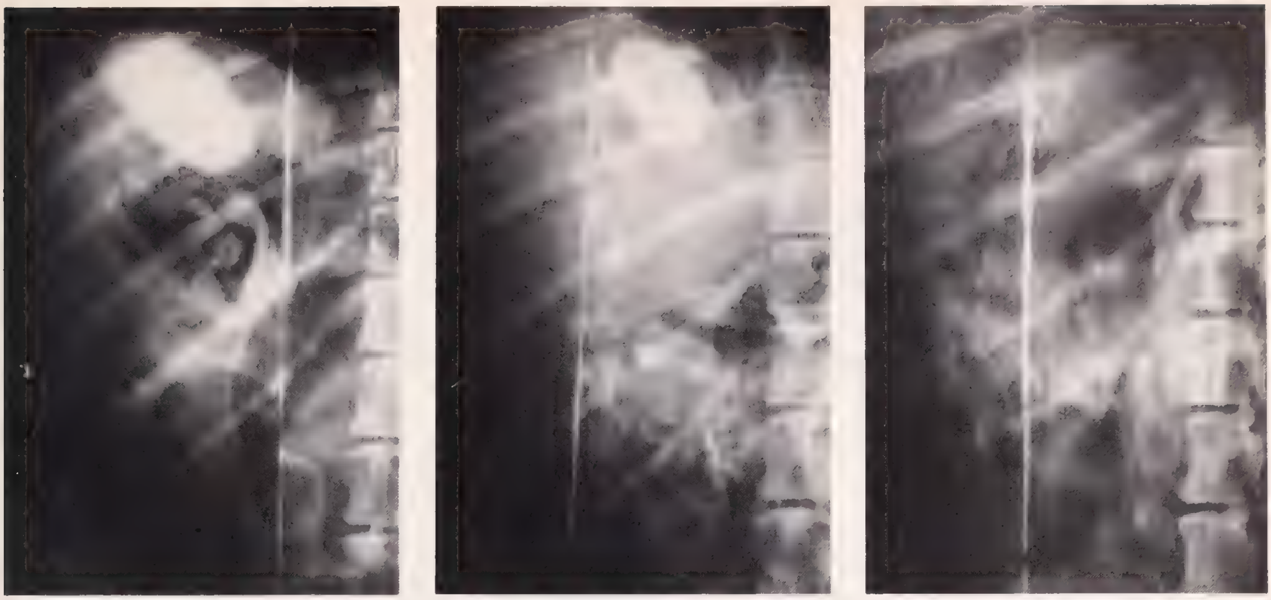


Fig. 3. Cholangiogram in one dog. **Left** Before Boyden meal; bile duct not distended. **Middle** One hour after Boyden meal. **Right** Two hours after Boyden meal (complete emptying of gallbladder).

perimental animals were fed with 5% glucose given subcutaneously (300 ml daily) and, following that, they were fed via the oral route, in the beginning with watery food and normal feeding after that. Antibiotic therapy (chloramphenicol, 0.5 gm/12 hr) was given in the first five postoperative days.

Liver function was assessed by means of liver tests, bilirubin, alkaline phosphatase and transaminases; pancreatic function was assessed by blood amylase test. Before the animals were killed, cholangiogram was carried out. Following death of the animals, the initial part of the jejunum together with the preserved area of the duodenum, the stump of the duodenum which remained peripheral to the pylorus, and a segment of the stomach as well as the extrahepatic system was obtained for macroscopic work-up. Also, a specimen from the liver and pancreas was obtained for histologic examination; histologic assessment was also made of the sphincter of Oddi and of the suturing area of the preserved segment of the duodenum, with the initial segment of the jejunum.

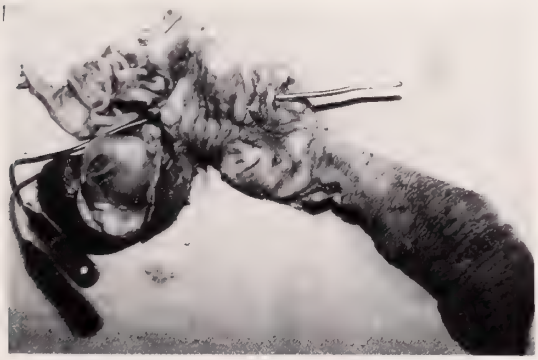


Fig. 4. Macroscopic presentation of viscera obtained after killing one dog; point of exit of Bakes' gall dilator shows position of sphincter of Oddi.

Results. The experimental animals were kept alive for 1–2 months. None of the animals presented any abnormality. In assessment of liver and pancreatic function, cholangiogram showed that the bile duct was not dilated and the gallbladder emptied normally (Fig. 3). No abnormal condition was observed in the macroscopic (Fig. 4) or microscopic examinations.

Discussion. The authors believe that these results are sufficient to conclude that if in duodenectomy in the dog, the area containing the sphincter of Oddi and the outlets of the pancreatic ducts is preserved, this area is viable and the functions of the sphincter of Oddi and the bile duct are accomplished normally. The viability of this area has been attributed to the possibility of preserving its vascularity.

The normal findings in the laboratory examinations of blood and the histologic examinations of the liver and pancreas are indicative of the fact that this technique does not influence hepatic and pancreatic function. The similarity of the anatomy and physiology of the intestinal and bile system of dogs and humans creates well-grounded hope that the method of duodenectomy described here will produce the same favorable results in humans as in dogs when duodenectomy is necessary to manage human diseases of the duodenum and pancreas.

Acknowledgments

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A New Monoclonal-Antibody-Defined Tumor Marker (KMO1) for Pancreatic Carcinoma

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Abstract

We performed biochemical and clinical studies on KMO1, a new marker for pancreatic cancer. The antigen was detected by a new monoclonal antibody, KMO1 antibody (KMO1-Ab), which was developed to an established human colon cancer cell line. The reversed passive hemagglutination reagent for this antibody was highly sensitive to sera from pancreatic cancer patients. The marker KMO1 has the following characteristics: (a) it differs from conventional tumor markers; (b) it is immunologically cross-reactive with CA19-9 and sialidase treatment of the two antigens reveals similar antigenic determinants; (c) it is a glycoprotein consisting of saccharide and protein and thus differs from CA19-9, which is a monosialoganglioside consisting of saccharide and lipid. The reversed passive hemagglutination method that we developed is easy to perform, does not require use of isotopes, has good specificity and reproducibility, and therefore should be clinically useful. Measurements of KMO1 with KMO1-Ab as a tumor marker for pancreatic cancer have sensitivity, specificity, and predictive value.

Various tumor markers for cancers of the digestive system have been studied but it has not always been possible to develop reliable screening tests (1, 2). With the advent of the monoclonal antibody technique, however, more specific and clinically useful tumor markers are being developed. In 1979 Koprowski and associates (3), using the hybridoma technique on the human colorectal carcinoma cell line SW1116, found a carbohydrate-linked antigen, which they named CA19-9. This antigen has been shown to be a good tumor marker for screening pancreatic carcinomas, and a radioimmunoassay kit for the antigen is now commercially available for clinical use (4, 5, 6, 7).

In our laboratories, a monoclonal antibody has been developed in mice against COLO-201, an established human colon carcinoma cell line (8). With this new antibody, we prepared a reversed passive hemagglutination (RPHA) reagent and characterized the antigen, which we refer to as KMO1. We found that KMO1 is chemically different from but immunologically reminiscent of CA19-9 and is an excellent marker for clinical screening of pancreatic carcinomas. With the RPHA technique the screening of patients' sera is easily accomplished without handling radioisotopes, which are essential for radioimmunoassays.

We describe here the immunologic and chemical characteristics of KMO1 and its potential clinical applications, particularly in comparison to CA19-9.

Materials and Methods

Preparation of Monoclonal Antibody (KMO1-Ab) against COLO-201. One hundred million

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cells of the colorectal carcinoma cell line COLO-201 were disrupted by sonication in 5 ml of phosphate-buffered saline (PBS) with an aprotinin concentration of 1000 units/ml, and the mixture was centrifuged for 30 min at 15,000 *g*. The resulting supernatant was loaded on a Sepharose 4B column to obtain low- and high-molecular-weight fractions. The high-molecular-weight fraction was emulsified in complete Freund's adjuvant and injected intraperitoneally into mice in a dose of 0.2 ml weekly. Four days after the fifth injection, the mice were killed to obtain a preparation of spleen cells. These immunized spleen cells were then fused with the mouse myeloma cell line P3-X63-Ag8-Ul (9) at a 4:1 ratio, using 45% polyethylene glycol (molecular weight 4000) according to the method of Galfre et al. (10). The resulting hybridomas were grown in hypoxanthine/aminopterin/thymidine medium. Supernatants from the growing hybridomas were screened for specific antibodies by an enzyme-linked immunosorbent assay as follows. The hybridoma culture supernatants were added to microplates coated with antigen (cultured human cancer cell lines or partially purified cancer-associated antigens). These plates were incubated for 1 h at 37°C, rinsed with PBS, converted with peroxidase-labeled antibody produced in rabbit against mouse immunoglobulins (IgA + IgG + IgM) (Zymed Lab., Inc.), and then incubated for 1 h at 37°C. The plates were washed with PBS, and *o*-phenylenediamine-H_2O_2 substrate solution was added. After incubation at room temperature for 30 min, the enzyme reaction was stopped with 2M H_2SO_4 and absorbance was read at 490 nm.

Hybridomas were cloned by propagation from a single cell by a limiting dilution procedure. Established hybridoma clones were injected intraperitoneally into pristane-primed BALB/c mice. After 10 to 14 days, the ascites that developed were collected. The specific monoclonal antibody (KMO1-Ab) in the ascites was purified by ammonium sulfate fractionation (45% saturation) and high-performance liquid chromatography (HPLC).

The purified KMO1-Ab was reacted by Ouchterlony's method (11) with rabbit antisera against mouse immunoglobulins (IgG_1, IgG_{2a}, IgG_{2b}, IgG_3, IgA and IgM) to determine the class of immunoglobulin.

Preparation of Reversed Passive Hemagglutination Reagent. By use of Imai's method (12), sheep red blood cells (SRBC) that were stabilized by glutaraldehyde were sensitized with the purified KMO1-Ab, washed several times with saline to remove excess KMO1-Ab, and lyophilized. The KMO1-Ab-sensitized sheep red blood cells (KMO1-RPHA) were reconstituted with phosphate buffer annexed to Antihebscell (Green Cross) to obtain a 0.5% suspension. The reconstituted KMO1-RPHA was stable for 2 weeks at 4°C.

Two sets of serial twofold dilutions of the test sample were prepared in phosphate-buffered saline supplemented with normal rabbit and guinea pig serum and stroma at pH 6.5 (PBS-stroma) in a U-cavity microtiter plate with 96 wells. To one set was added 1 drop (25 μl) of PBS-stroma, and to the other set 1 drop of PBS-stroma containing KMO1-Ab. After being thoroughly shaken on a micromixer, the plate was covered and allowed to stand for 20–60 minutes at 37°C. After this incubation, 25 μl of KMO1-RPHA was added to each well. Then the plate was shaken again on a micromixer and allowed to stand for 1.5–2 hours at room temperature. The pattern of hemagglutination was read, and the titer was expressed as the highest dilution of the sample that showed hemagglutination in the rank to which PBS-stroma was given. The reaction was estimated to be specific when the hemagglutination was inhibited in the presence of KMO1-Ab. When agglutination in the rank to which KMO1-Ab was added was inhibited in comparison with the rank to which PBS-stroma was added, over 2 wells, 1 well, or none, the sample was judged "KMO1 positive," "pending," or "negative," respectively. Each serum concentration was measured 10 times to judge the reliability of measurements. Intra-assay variation tests were performed, and the variation among three technicians using various KMO1 concentrations of serum was also assayed.

Purification and Chemical Analyses of KMO1. The supernatant obtained by centrifugation and filtration of COLO-201 culture broth was concentrated about 38-fold with macrosolute concentrators (Minicon, Type B15, Amicon). The concentrated solution (3 ml) was applied on the KMO1-antibody-bound Sepharose 4B column (5.6 ml), which had been equilibrated with 10 mM phosphate buffer, pH 7.7. The column was washed with the same phosphate buffer and then with the same buffer containing 0.5 M NaCl. The adsorbates on the column were then eluted with 3 M guanidine-HCl solution at room temperature, and the eluted fractions that appropriately reacted with KMO1-RPHA were collected and dialyzed against phosphate-buffered saline (pH 7.4) containing 0.1% sodium azide at 4°C for 2

TABLE 1

Quantitative Determination of KMO1 and CA19-9 in Supernatant Fluids from Cultures of Various Human Cancer Cell Lines

Cell lines	Cancer type	Days*	KMO1-RPHA titer†	CA19-9‡ (units/ml)
SH-1	esophageal	4	<2	negative
PC-1	lung	4	<2	negative
PC-3	lung	3	2,048	>120
PC-9	lung	3	<2	negative
PC-10	lung	4	<2	negative
G-415	gall bladder	3	<2	negative
HEp-2	laryngeal	3	<2	negative
KB	oral	2	<2	negative
NRC-12	renal	3	<2	negative
NBT-2	bladder	4	<2	negative
J-111	monocytic leukemia	2	<2	negative
HL-60	acute promyelocytic leukemia	2	<2	negative
MKN-28	stomach	3	<2	negative
MKN-45	stomach	4	4	negative
KATO-III	stomach	4	16	>120
COLO 320_{DM}	colon	3	<2	negative
COLO 201	colon	4	256	>120
Medium solely	—	—	<2	negative

* Cultured for time period indicated.

† KMO1 detection was performed with KMO1-RPHA reagent.

‡ CA19-9 in each supernatant was detected by radioimmunoassay (RIA).

days. Eluted and dialyzed KMO1 was titrated with KMO1-RPHA reagent in each experiment.

For analyses of the sugar and protein contents of the purified KMO1, the dialyzed KMO1 was diluted 6 times with phosphate-buffered saline (the RPHA titer of the diluted KMO1 was 1:128; that is, the RPHA titer of the dialyzed KMO1 used originally was 1:768). Sugar content was determined quantitatively by the anthron-sulfuric acid method (13) with mannose as a standard. Protein content was determined by the method of Lowry et al. (14) with bovine serum albumin as a standard.

Thin-layer chromatography (TLC) and high-performance thin-layer chromatography (HPTLC) of KMO1 were performed to determine whether gangliosides such as those found in CA19-9 were contained in this material (15). KMO1 concentrated by dialysis (RPHA titer 16,000, 50 μl) and monosialoganglioside G_{M1} ($G.G_{M1}$, Seromed, 15 and 200 μg for TLC and 32, 16, 8, 4, and 2 μg for HPTLC) were spotted on a precoated TLC plate (Silica Gel 60, Merck). Each sample on the plate was developed with a chloroform-methanol-water solvent (55:45:10 by volume) containing 0.02% $CaCl_2$ at room temperature for 1.5 hours. The color of each migrated spot was developed by standing the TLC plate in an iodine vapor (16). After the color disappeared, anthron-sulfuric acid reagent was sprayed on the plate to visualize the sugar-containing substances. Likewise, amino groups were visualized with ninhydrin reagent (17).

Immunologic Characterization of KMO1. The immunologic characterization of KMO1 was threefold:

(1) Reactivity of KMO1-RPHA with various cancer cell lines in culture. Seventeen different types of malignancies that are established in cell culture lines were examined (Table 1). After several days of culture in appropriate media, each culture was filtered and the supernatant was reacted with KMO1-RPHA as described above. A standard culture medium was used as a control. For comparison, each supernatant was also examined for CA19-9 with a commercial radioimmunoassay kit (Green Cross).

(2) Comparison of KMO1 to other tumor markers. Six known tumor markers were compared. Reactivity of KMO1 was examined by using commercial radioimmunoassay kits for carcinoembryonic antigen (CEA) (Abbott), ferritin (Abbott), calcitonin (Dai-ichi Isotope Labs), human chorionic gonadotropin (hCG) (Green Cross), β-2-microglobulin (Pharmacia), and α-fetoprotein (AFP) (Eiken Chemical). Inhibitory effects of antibody to human AFP (Green Cross) and rabbit antiserum against human β-2-microglobulin (Seikagaku Kogyo) were also examined by adding these substances in appropriate dilution to the assay system for KMO1.

Special attention was given to possible cross-

TABLE 2
Sensitivity of Each Tumor Marker in Various Conditions

Disease	KMO1-RPHA	CA19-9	CEA No. (%)
Pancreas cancer	34/46 (79.3)	36/44 (81.8)	12/29 (41.4)
Chronic pancreatitis	5/25 (20.0)	4/25 (16.0)	5/23 (21.7)
Esophageal cancer	2/30 (6.7)	1/30 (3.3)	2/28 (7.1)
Gastric cancer	8/49 (16.3)	10/51 (19.6)	7/29 (24.1)
Common bile duct cancer	10/20 (50.0)	12/20 (60.0)	1/5 (20.0)
Colorectal cancer	14/44 (31.8)	15/43 (34.9)	17/35 (48.6)
Hepatoma	13/26 (50.0)	3/27 (11.1)	14/22 (63.6)
Breast cancer	3/18 (16.7)	2/18 (11.1)	2/9 (22.2)
Esophageal varix	1/16 (6.3)	0/4 (0)	3/6 (50.0)
Benign diseases	0/16 (0)	0/9 (0)	—
Normal	0/73 (0)	0/8 (0)	—

reactivity with CA19-9 antigen. The KMO1 antibody was added to different dilutions (1:10 to 1:10,000) to the radioimmunoassay system for CA19-9. The CA19-9 used in this study was supplied in the kit as the calibration standard (60 units/ml) and was assayed by the method of Koprowski et al. (3, 5). As a control, the mouse monoclonal antibody against human hepatitis B surface antigen (ID6) was added to the assay system in lieu of the KMO1.

(3) Antigenicity of KMO1 after enzyme treatments. The KMO1 was treated with three different enzymes: sialidase of *Clostridium perfringens,* Type V (Sigma, 0.22 units/ml); trypsin of bovine pancreas, Type III (Sigma, 4.4 μg/ml); and Pronase P (Kaken Kagaku, 93.5 μg/ml). The sialidase treatment was performed in 0.1 M acetate buffer (pH 4.5) at 37°C for 2 hours, and the trypsin and pronase treatments were done in 50 mM Tris-HCl buffer (pH 8.1) at 37°C for 17 hours. The reaction was stopped by rapidly freezing these mixtures, and residual antigenicity was measured by KMO1-RPHA. For comparison, the same enzyme treatments were performed on the standard solution of CA19-9 included in the RIA kit. The residual antigenicity of CA19-9 was determined by the radioimmunoassay.

Clinical Studies. We performed two clinical studies:

(1) Immunohistochemical reactivities of KMO1 antibody on human tissues. Selected cases of pancreatic diseases including carcinomas and some colon cancers were studied. Neoplastic or nonneoplastic lesions and adjacent tissues were obtained during surgery at the Kobe University Hospital. Paraffin sections (4–6 μm) were made from these surgical specimens and were reacted with the monoclonal KMO1 antibody by the peroxidase-antiperoxidase method as described by Sternberger (18).

(2) Evaluation of KMO1 as a tumor marker in blood screening. Blood samples were collected from patients at the time of their admission to our service in the Kobe University Hospital. Immediately after the collection, each sample was centrifuged, and the sera obtained were stored at −80°C until use. Sera from 290 patients and 73 healthy subjects (controls) were screened with KMO1-RPHA. The disease categories and number of patents examined in each category are listed in Table 2. Diagnoses were established and/or confirmed histopathologically on surgically removed specimens. For comparison, the commercial radioimmunoassay kits for CA19-9 and CEA were used to determine these tumor markers in the same patients.

Results

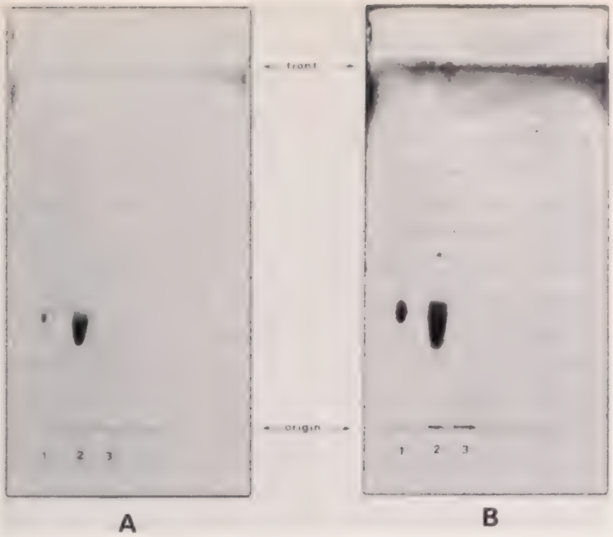
KMO1-Ab and RPHA Measurements. As revealed by Ouchterlony's method, the monoclonal antibody, KMO1-Ab, reacted with antiserum against mouse IgG_1. The result indicates that KMO1-Ab is an IgG_1.

As a rule, RPHA measurements were performed by three different individuals 10 times each on each sample. The coefficient of variation ranged from 6% to 9%, and individual differences were 3% to 10%. These figures suggest that the KMO1-RPHA method is reliable for assay.

Chemical Characteristics of KMO1. The purified KMO1 (RPHA titer 1:768) had a carbohydrate content of 3.5 μg/ml and a protein content of 27 μg/ml as determined by the anthron-sulfuric acid method and Lowry's method, respectively. On the other hand, neither TLC (Fig. 1) nor HPTLC (Fig. 2) detected monosialoganglioside (G G_{M1}) as a lipid component in KMO1, indicating that KMO1 is chemically different from CA19-9.

Immunologic Characteristics of KMO1. Among malignancies of the digestive system, one stomach carcinoma cell line (KATO-III), in addition to line COLO-201, exhibited a high RPHA titer (Table 1). Surprisingly, one lung cancer line (PC-3) showed an unexpectedly high titer. Concomitantly performed radioimmunoassays for CA19-9 showed results remarkably similar to those with KMO1-RPHA, indicating an antigenic similarity between KMO1 and CA19-9.

In respect to comparison of KMO1 to other tumor markers, the purified KMO1 was negative



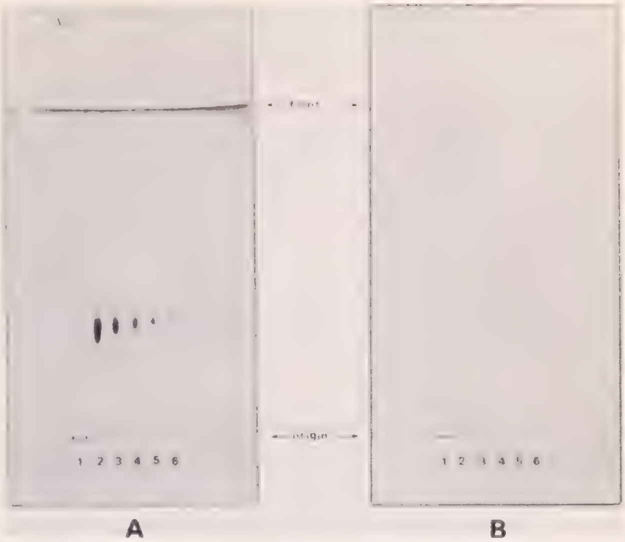


Fig. 1. Left Thin-layer chromatography of KMO1. (A) Lanes 1 and 2, monosialoganglioside G_{M1}, 15 μg and 200 μg, respectively; lane 3, KMO1 (RPHA titer 16,000), 50 μl. Plate was developed with a chloroform-methanol-water solvent and stained with iodine vapor. (B) Same as plate (A) except that plate was stained with anthrone-sulfuric acid reagent. **Fig. 2. Right** Thin-layer chromatography of KMO1 with HPTLC plate. (A) Lane 1, KMO1 (RPHA titer 16,000) 50 μl; lanes 2, 3, 4, 5, and 6; monosialoganglioside G_{M1}, 32, 16, 8, 4, and 2 μg. Plate was developed with chloroform-methanol-water and stained with iodine vapor. (B) Same as plate (A) except that plate was stained with ninhydrin reagent.

to all radioimmunoassays for CEA, ferritin, calcitonin, hCG, β-2-microglobulin, and AFP. Likewise, addition of either horse antibody against human AFP or rabbit antiserum against human β_2-microglobulin did not affect the KMO1-RPHA assay system. These results indicate that KMO1 is different from these conventional tumor markers. On the other hand, addition of KMO1 antibody to the CA19-9 assay system resulted in suppression of CA19-9 values in inverse proportion to the concentration of the antibody. Antibody against human hepatitis B did not affect the CA19-9 assay system (Fig. 3). These findings emphasize the antigenic similarity between KMO1 and CA19-9.

As shown in Table 3, the antigenicity of KMO1 was lost after sialidase treatment but unchanged after trypsin or pronase treatment. This indicates that the antigenic determinant region of KMO1 consists of the sialo group without protein. The antigenicity of CA19-9 was affected similarly by these enzymes. These results suggest that the antigenic determinant regions of KMO1 and CA19-9 have similar chemical compositions.

Clinical Studies. In the immunohistochemical studies (Fig. 4), a strongly positive reaction was noted in the cytoplasm of pancreatic carcinoma cells. Although acinar cells, the epithelium of main pancreatic ducts, and islet cells were generally negative in normal pancreatic tissues, the intralobular ducts and centroacinar cells exhibited variable degrees of positive reaction. In cases of islet hyperplasia, some positive cells were found in the islets (Fig. 5). Colorectal carcinoma cells showed only occasional weak positivity.

Reactivity of KMO1-RPHA with patient

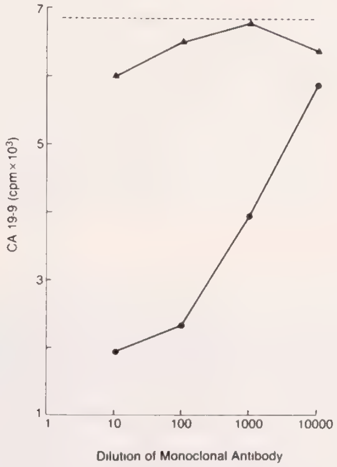


Fig. 3. Inhibitory effect of KMO1-Ab on binding of CA19-9 to its target antigen. CA19-9 (60 units/ml) used was the calibration standard provided in the RIA kit. CA19-9 was determined quantitatively by a method described elsewhere (5). The curves represent changes in radioactivity of CA19-9 after addition of appropriate dilutions of monoclonal antibodies KMO1 and ID6, respectively. Broken line denotes radioactivity of control CA19-9, without addition of any antibody.

TABLE 3

Changes in Antigenicity of KMO1 after Treatment with Sialidase and Protease

	KMO1-RPHA titer[1]		CA19-9 RIA[2] (units/ml)	
Enzyme	Untreated	Treated	Untreated	Treated
Sialidase	512	2	1,200	negative
Trypsin	512	512	1,200	1,200
Pronase	512	512	1,200	1,200

KMO1 treated with or without each enzyme was determined with (1) KMO1-RPHA and (2) CA19-9 RIA.

sera: Sera from the patients with carcinoma of the pancreas gave a positive reaction with KMO1-RPHA in 79.3% of the cases, somewhat lower than the 81.8% positive rate in the CA19-9 radioimmunoassay (not a statistically significant difference). Sera from patients with chronic pancreatitis showed no difference in the percentage of positive reactions among the three tumor markers. Sera from colon cancer patients gave a 31.8% positive ratio with KMO1-RPHA and a 34.5% positive ratio with CA19-9. A large difference in the positive ratio between KMO1-RPHA and CA19-9 was observed in the sera from hepatoma patients (Table 2).

The reliability of KMO1-RPHA in differential diagnosis for pancreatic cancer was similar to that of CA19-9 in terms of sensitivity, specificity, and predictive value (Fig. 6).

Correlation between KMO1-RPHA titers and CA19-9 values (units per milliliter) were compared in the sera from patients with pancreatic carcinoma and chronic pancreatitis, and a good correlation was obtained ($r = 0.867$; $p < 0.01$) (Fig. 7).

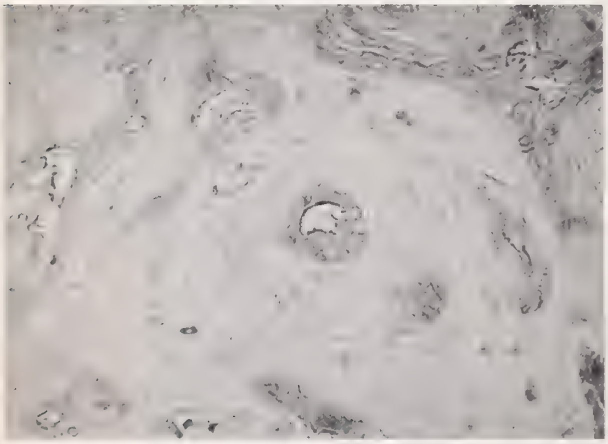
Discussion

We immunized mice with a high-molecular-weight fraction from cells of an established human colon cancer cell line (COLO-201) and developed a hybridoma that produced a monoclonal antibody, KMO1-Ab. In addition to the supernatant from COLO-201, supernatants from cultures of established lung and gastric cancer cell lines reacted with KMO1-Ab, indicating that KMO1 is a secretory antigen that acts as a tumor marker. Histochemical investigation showed that KMO1-Ab reacted with some pancreatic cancer tissue, epithelium of the pancreatic ducts in normal pancreatic tissue, and some centroacinar cells.

The specificity of KMO1 as a tumor marker was studied. KMO1 was not neutralized by antisera against AFP and β_2-microglobulin, and AFP, CEA, ferritin, calcitonin, and hCG were not detected in purified KMO1 preparations. These results suggest that KMO1 is a new tumor marker different from the other tumor markers.

We prepared an RPHA reagent with the antibody and used it for biochemical and clinical studies. The specificity of the test was confirmed by inhibition studies with the specific antibody. Intra-assay and intertechnician reproducibility were good, with a coefficient of variation less than 10%.

The characteristics of KMO1 were studied in comparison with those of CA19-9. Antibody against CA19-9 (CA19-9-Ab) has been reported to be an IgG_1 (5). The KMO1-Ab was found to be an IgG_1 in the present study. Tests of cross-reactivity of KMO1-Ab with CA19-9 showed that CA19-9 was neutralized by KMO1-Ab but not by antibody to human hepatitis B. The facts that CA19-9 titers were suppressed in the presence of



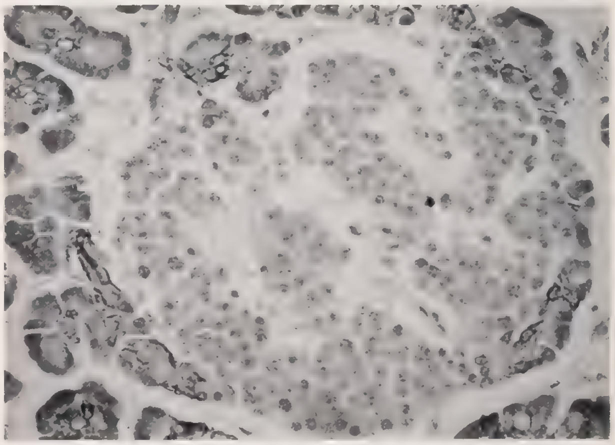


Fig. 4. **Left** Tissue section from a patient with pancreatic cancer. Cancer cells have positive granules in cytoplasm. Fibers and cellular component in matrix are negative for KMO1. Peroxidase-antiperoxidase (PAP) staining with KMO1-Ab. Fig. 5. **Right** Tissue section from a patient with islet cell hyperplasia of pancreas. Centroacinar and intralobular ductular cells show positive granules. Islet and acinar cells have no positive granules. PAP staining with KMO1-Ab.

KMO1-Ab and that purified KMO1 reacted with CA19-9 indicated that KMO1-Ab and CA19-9 have common antigenic determinants.

Koprowski et al. (5, 6, 19) showed that CA19-9 loses antigenic activity after sialidase treatment, that it does not contain protein in the antigenic region, and that it is a monosialoganglioside. It was shown that the antigenic determinant is sialylated lacto-*N*-fucopentaose II (19). KMO1 was inactivated by sialidase treatment but not by protease treatment, demonstrating that a sialo group is present in the region of the antigenic determinant.

Magnani et al (19, 20) have made it clear that CA19-9 is a monosialoganglioside. We analyzed the lipid content of purified KMO1 by the TLC method of Magnani et al. but found no evidence that KMO1 is the same as CA19-9. The detection limit for lipid (monosialoganglioside: $G.G_{M1}$) was 2 μg. The concentration of purified KMO1 used in the test was 3.5 × 16,000/768 × 50/1000 in sugar and 27 × 16,000/768 × 50/1000 in protein, namely a total of 31.75 μg.

We conclude that even if monosialoganglioside was present at a concentration undetectable by TLC, it is not the main constituent of KMO1. It is likely that KMO1 and CA19-9 both contain the antigenic determinant commonly recognized by KMO1-Ab and CA19-9-Ab but that the CA19-9 itself consists of monosialoganglioside, carbohydrate and lipid, whereas KMO1 consists of carbohydrate and protein. Thus, the antigens are different.

KMO1 and CA19-9 show immunologic cross-reactivity, implying that the clinical usefulness of KMO1 would be similar to that of CA19-9. Serum samples from patients with pancreatic carcinoma were positive for KMO1 in 79% of the cases, a little lower than the rate of 82.5% for CA19-9, (not a statistically significant difference), whereas in serum samples from patients with other diseases, including chronic pancreatitis, the percentage of positive results was almost the same except for sera from hepatoma patients. Diagnoses of pancreatic cancer with either the KMO1-RPHA or the CA19-9 kit did not reveal any significant difference in sensitivity, specificity, or predictive value. Furthermore, KMO1-RPHA and CA19-9 values agreed well, with a correlation coefficient of 0.867 ($p < 0.01$).

The development of KMO1-RPHA is clinically significant. The test does not require special equipment such as that needed for radioactivity assays, it is easy to perform, and it has good reproducibility.

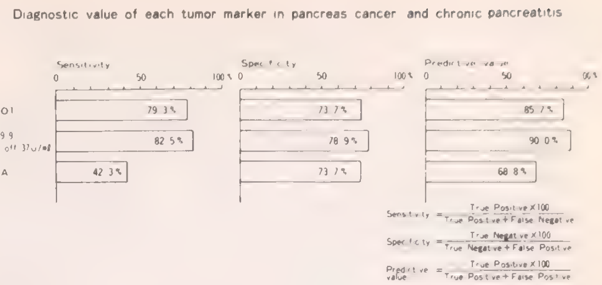


Fig. 6. Diagnostic value of tumor markers in pancreatic cancer and chronic pancreatitis.

Summary

KMO1 is a new tumor marker that is different from conventional tumor markers. The KMO1 and CA19-9 antigens exhibit immunologic cross-reactivity and their antigenic determinants are almost identical. KMO1 is a glycoprotein, whereas CA19-9 is a monosialoganglioside consisting of carbohydrate and lipid. Our KMO1-RPHA method is easy to perform, does not

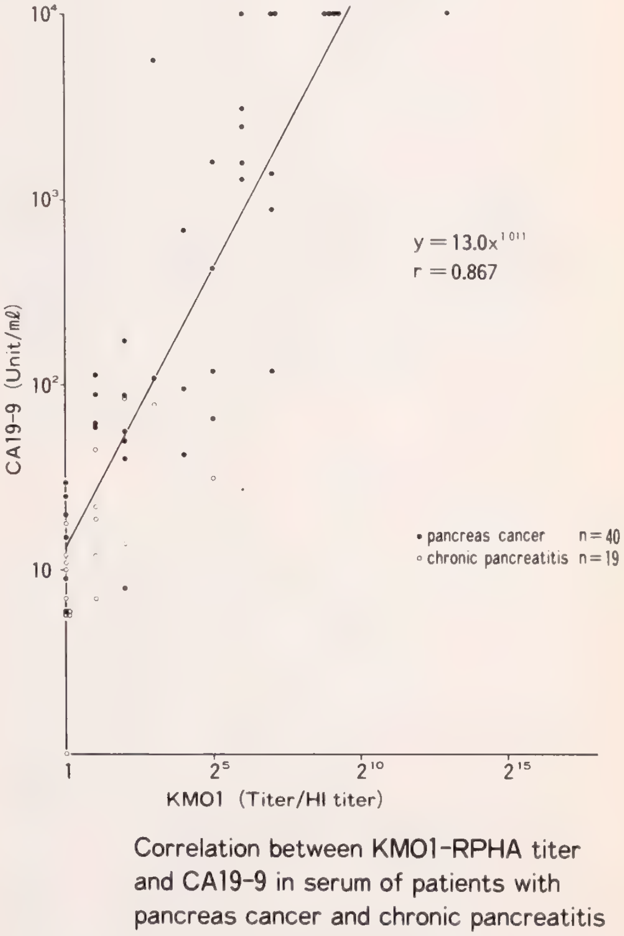


Fig. 7. Correlation between KMO1-RPHA titer and CA19-9 concentration in sera from patients with pancreatic cancer and chronic pancreatitis.

require use of isotopes, and has good specificity, sensitivity, and reproducibility in clinical studies.

Acknowledgments

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Carcinoma of the Esophagus: Surgical Treatment with Low Operative Mortality and Low Rate of Anastomotic Leakage

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Abstract

Esophagogastrectomy with esophagogastrostomy (E-G) as a one-stage procedure is considered a high-risk surgical procedure because of the high rate of anastomotic leakage and the high operative mortality. A total of 80 patients among 246 with carcinoma of the esophagus seen at the Bronx VA Medical Center between January 1, 1970 and December 31, 1984 underwent E-G, with an operative mortality of 11.2% (9 of 80). Anastomotic leakage occurred in 3 patients, one fatal and 2 nonfatal. No leakage occurred from an intrathoracic anastomosis for the last 12 years of the study period (62 consecutive cases). The most common cause of operative mortality was respiratory failure. Long-term prognosis was poor. We conclude that E-G can be done safely by carefully observing fundamental surgical principles.

Approximately 9,000 patients die from carcinoma of the esophagus annually in the United States (1). There has been little change in the five-year survival rate for the past few decades (1). Two main reasons for this grave prognosis are the late discovery of the disease and a lack of curative treatments (2–4). At present, the surgical treatment—esophagogastrectomy with esophagogastrostomy—is the most effective means of palliative treatment. The surgery, however, must be done with a low operative mortality and morbidity (5–7). In the past, this surgery has been associated with a fairly high operative mortality and morbidity (8), usually because of the high rate of leakage from the intrathoracic anastomosis (9–12).

This paper presents a review of our experience with 80 consecutive esophagogastrectomies with esophagogastrostomy as a one-stage procedure. All patients were operated on by the surgical resident staff under direct supervision of one of us. Our experience shows that by carefully observing fundamental surgical principles, this surgery can provide good palliation and can be done safely with an acceptable operative mortality and a low leakage rate without extraordinary surgical dexterity.

Materials and Methods

Tumor registry and operative reports between January 1, 1970 and December 31, 1984 at Bronx VA Medical Center were reviewed. A total of 246 patients (Table 1) were seen in this period with a diagnosis of carcinoma of the esophagus, including carcinoma of the cardia with extension into esophagus. Carcinoma of other parts of the stomach, such as the fundus, were excluded, even though esophagogastrostomy was a part of the surgery. A total of 160 patients underwent surgery other than diagnostic procedures, in operations ranging from a simple feeding gastrostomy to an esophagogastrectomy with primary esophagogastrostomy. Of these 160 patients, 80 underwent esophagogastrectomy with esophagogastrostomy as a one-stage procedure. This series of

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TABLE 1
Treatment

Treatment	No.
Surgery	160
Esophagogastrectomy	80
Bypass without resection	18
Endoesophageal intubation	26
Gastrostomy	35
No Surgery	86
Total	246

80 consecutive procedures is the subject of this paper.

Two additional patients needed an emergency esophagectomy for perforation of the esophagus during diagnostic endoscopy, but reconstruction of the gastrointestinal tract was not performed. A total of 18 patients underwent various types of bypass procedures without esophagectomy. Endoesophageal intubation was performed in 26 patients, and 35 patients were treated with feeding gastrostomy with or without cervical esophagostomy.

Clinical Features. All patients in this series were male. Twenty-eight were whites, 49 blacks, and 3 Hispanics. The average age of the entire group was 55.9 years old (ranging from 38 to 83). The average was 61.4 years for whites (range, 42 to 83), 55.2 for blacks (range, 38 to 74) and 58 for hispanics (range, 47 to 67).

All patients were diagnosed preoperatively either by cytologic or histologic study, except for one patient who was found to have adenocarcinoma during an attempted myotomy for achalasia. Of the 80 patients, 62 were found to have squamous cell carcinoma and 18 had adenocarcinoma. Five patients had upper one-third lesions, 30 had midesophageal lesions, and 45 had lower one-third lesions.

All patients but 3 were studied for dysphagia and weight loss, which ranged from a few pounds to 40 lb (average, 20 lb). The severity of dysphagia ranged from regular diet intolerance to liquid intolerance. Three patients were diagnosed incidentally during work-up for unrelated gastrointestinal complaints, such as right upper quadrant pain.

Preoperative evaluation and preparation included routine CBC, SMA-18, prothrombin time, upper gastrointestinal series, chest x-rays, ECG, and pulmonary function test with arterial blood gas studies. Radioisotope scans were used until 1981, when CT scan with contrast material, including the upper abdomen, eliminated the necessity for liver scan. Esophagoscopy with biopsy and/or cytologic studies were performed as a routine procedure. Bronchoscopy was performed for selected patients. Nutritional evaluation, including skin tests, were performed in the last several years. Maximum efforts were made to increase caloric intake by oral intake or by nasogastric feeding prior to surgery. Total intravenous hyperalimentation was given when other means failed. Anemia was corrected by transfusion.

The majority of the 80 patients did not receive any form of adjunctive treatment. Selection of those who did was made at the Surgical Tumor Board, case by case. Five patients received various doses of preoperative radiotherapy, up to 6,400r; 12 patients received postoperative radiation to the mediastinum ranging from 800 to 4,600r. One patient received a course of chemotherapy, and one other had a combination of chemo- and radiotherapy postoperatively. From April 1982 to the end of the study period (December 1984), a preliminary protocol of preoperative combined chemo- and radiotherapy was set up for squamous cell carcinoma (details are discussed below). A total of 6 patients underwent the entire course. In addition, one patient received a course of chemotherapy as part of the protocol, but refused a course of radiotherapy.

Surgical Techniques. Several different incisions were used (Table 2). A left thoracotomy alone was used in 2 patients. The left chest cavity was entered through the 6th intercostal space with the patient in the right lateral position. The abdominal cavity was entered through the esophageal hiatus with a radial incision of the diaphragm. The entire abdominal portion of the procedure, including the mobilization of the duodenum and pyloroplasty, were performed via this incision. In 3 patients a midline abdominal incision, right thoracotomy, and cervical incision were used. In this technique, the esophagus was mobilized and excised in the right chest. The stomach was mo-

TABLE 2
Type of Incision

Incision	No.	Leakage	Death
Rt. thoracotomy & abdominal	61	1	6
Left thoracoabdominal	9	1	1
Left thoracotomy only	2	0	1
Without thoracotomy	5	1	1
Rt. thoracotomy, abdominal & cervical	3	0	0
Total	80	3	9

bilized by the laparotomy and brought up to the neck substernally, except for one patient, whose stomach was placed on the esophageal bed. Five patients were operated on without thoracotomy, using the abdominal and cervical incisions only. The left thoraco-abdominal incision was utilized in 9 patients. In the majority of the cases, an oblique incision over the thoracic wall and abdomen was used, entering the left chest cavity through the 7th intercostal space by dividing the costal cartilage. In some cases, the midline abdominal incision was extended over the left 7th or 6th intercostal space.

The most common procedure was the classic Ivor Lewis approach (13), either in one position or separate positions. A total of 61 patients were operated on by this approach (in 3 patients, a one-position approach was used). The right chest was entered through either the 5th or 6th intercostal space, depending on the anticipated level of the anastomosis.

The general operative technique included a double lumen endotracheal tube, used whenever possible with one-lung anesthesia during dissection of the esophagus and while performing the anastomosis. The abdominal portion of the procedure, that is, mobilization of the stomach, was carried out in the standard fashion, preserving the right gastric artery and the arcade of right gastroepiploic artery as high as possible toward the left. The esophageal hiatus was widened as much as possible and the distal esophagus was mobilized as high as possible. It is impossible to overemphasize the need for gentle handling of the tissues and extreme care in not injuring the proximal part of the stomach at this stage of surgery. The duodenum is mobilized to the beginning of the 4th portion by Kocher's maneuver. A drainage procedure, either pyloroplasty or pyloromyotomy, was performed in all cases. In cases of abdominal incision and right thoracotomy, the abdominal incision was closed and the patients were repositioned for the right thoracotomy in a majority of the cases. In a few cases, the patient was placed in the 45° oblique position and the entire surgery was performed without changing the patient's position.

The thoracic portion of the surgery included excision of the esophagus and anastomosis. After the esophagus is mobilized, the stomach is brought up into the pleural cavity by gentle traction. The stomach is transected just distal to the G-E junction or distal enough to clear the tumor, using a stapler. The staple closure was reinforced by a running seromuscular suture. The esophagus was transected above the azygos vein, level with a 10-cm proximal margin whenever possible.

Excessive mobilization of the proximal esophagus was avoided to preserve a good blood supply to the esophageal stump. No proximal occluding clamp was used. Pleura over the proximal esophagus was not mobilized excessively.

All anastomoses were performed in the end-to-side anastomosis fashion, either in the thoracic cavity (72 cases), or in the neck (8 cases). The intraluminal circular stapler was used in 7 cases operated on from November 1983 to the end of the study period. Manual anastomosis was performed in the other 73 cases.

Manual anastomosis can be done either prior to or following transsection of the esophagus, whichever is easier. The site of anastomosis is near the upper end of the stomach. The most important consideration is preservation of a good blood supply to the anastomotic site. The posterior wall of the esophagus is sutured to the anterior wall of the stomach with a row of interrupted mattress sutures of 4-0 nonabsorbable sutures. These sutures are placed in the seromuscular layer of the stomach and muscle layer of the esophagus. After completion of this layer, a linear incision, about equal to the diameter of the esophagus, is made through the anterior wall of the stomach, 5 mm away from the previous suture line. Use of the electric cautery provides satisfactory hemostasis. The posterior wall of the esophagus is opened, if not transsected yet.

A row of interrupted, nonabsorbable sutures are placed through the full thickness on the both sides. All sutures are tied inside the lumen. Transsection of the esophagus is completed. A nasogastric tube is carefully advanced into the distal part of the stomach under direct vision. The first layer of the anterior suture line is a row of full thickness 4-0 interrupted nonabsorbable sutures. These sutures are placed so that when tied, the knots lie within the lumen of the stoma. The second layer of the anterior suture line is also interrupted 4-0 nonabsorbable suture catching the seromuscular coat of the stomach and muscular layer of the esophagus. These sutures are placed in a U shape, starting on the gastric side vertically and transversely on the esophagus and returning to the stomach. After completion of this layer, the suture line is reinforced by fundoplication and/or a pleural flap or omental flap.

Intraluminal circular stapler anastomosis: The esophagus has to be transsected prior to anastomosis in this technique. After the esophagus is transsected, a purse-string suture of 0-

monofilament suture is applied to the esophagus, about 5 mm proximal to the stump. It is most important to place this suture through the entire thickness of the esophagus. Traction sutures of 3-0 monofilament suture are placed at the four corners of the esophageal stump. It is, again, essential to include the entire thickness of the esophagus. The stapler is inserted, without a cap, into the lumen of the stomach through an opening on the anterior wall of the stomach and pushed against the stomach wall at the proposed anastomotic site. A purse-string suture is applied around the shaft of the stapler. An opening is made in the stomach wall and the shaft of the stapler is pushed through this opening. The purse string suture on the stomach side is tied. The cap of the stapler is placed on the shaft, and the entire device is inserted into the lumen of the esophagus. Extreme care should be taken not to separate the esophageal mucosa from the muscle layer of the esophagus. The previously placed four traction sutures are helpful in this regard. The esophageal purse-string suture is tied and the traction sutures are removed. The staple is fired. The instrument is removed. A nasogastric tube is gently advanced into the stomach by the anesthesiologist. The opening in the stomach is closed by a stapler. The anastomotic line is also reinforced as described above.

Additional surgery was performed on 13 of the 80 patients. One patient had a biopsy for a mass lesion in the right middle lobe which turned out to be a benign granuloma. From December 1982 to the end of the study period, a needle jejunostomy was performed on 12 patients.

Postoperative management began with extubation carried out as soon as feasible, most of the time within 24 hr. The nasogastric tube was kept in place and connected to the low, intermittent suction until the patient was ready for oral feeding. A sump-type nasogastric tube decompresses the stomach better than a conventional Levin-type tube. Two chest tubes are left in place and connected to suction until oral feeding begins. The patients were not orally fed until the anastomotic site was examined by esophagram. Intravenous fluids, 2–3 L daily, were given as the maintenance fluids. Blood transfusions and colloidal solutions were given as needed. Total hyperalimentation was given to a few patients. The jejunostomy feeding was begun on the first postoperative day for patients with a needle jejunostomy. Perioperative antibiotics were used for all patients.

The anastomotic site was examined on the seventh or eighth postoperative day by cine-esophagogram, using gastrographin. Oral feeding was begun when the study showed no leakage.

TABLE 3
Complications

Complication	No.
Splenic injury	23
Anastomotic leakage	3
Tracheal injury	1
Azygos vein injury	1
Aortogastric fistula	1
Small-bowel obstruction	1
Total	30

Results

Complications. The most common intraoperative complication was injury to the spleen, requiring splenectomy in 23 patients (Table 3). Mild to moderate degrees of atelectasis and benign atrial arrhythmia occurred in about 50% of the patients. One patient sustained an injury to the posterior wall of the trachea, which was repaired using the gastric wall. Another patient sustained a laceration of the azygos vein during esophagectomy without thoracotomy. The injury was repaired by open thoracotomy. One patient developed an episode of small-bowel obstruction due to adhesions 20 days following his surgery.

Anastomotic leakage occurred in 3 patients, fatally in one. One of the other two patients with anastomotic leakage had had esophagectomy without thoracotomy and developed a small leak from the suture line in the neck which closed spontaneously in a few days. The second nonfatal case of anastomotic leakage was due to a chest tube erosion into the gastric stump closure line; withdrawing the tube resolved the problem. The one fatality from anastomotic leakage is discussed below.

Another complication was aortogastric fistula, resulting in a massive fatal hemorrhage; this case is also discussed below.

Mortality. Operative mortality (defined as death within 30 days of surgery) occurred in 9 patients (11.2%) (Table 4). Anastomotic leakage was responsible in only one patient, an 83-year-old man with adenocarcinoma of the lower esophagus. The surgery was performed through a left thoracoabdominal incision. Leakage occurred on the 5th postoperative day. The patient was managed conservatively and died on the 15th postoperative day because of sepsis. Massive bleeding due to an

TABLE 4
Mortality

Case No.	Year	Cause
1	1970	Anastomotic leakage
2	1971	Mucous plug in trachea
3	1972	ARDS
4	1980	Sudden cardiac death
5	1981	Azygos vein injury
6	1982	ARDS
7	1982	ARDS
8	1982	ARDS
9	1984	Aortogastric fistula

ARDS, Adult respiratory distress syndrome.

TABLE 5
Survival by Race and Cell Type

Survival (mo)	Race*			Cell type*		
	White	Black	Hisp.	A	S	Total
1†	4	5		2	7	9
<12	13	27	1	9	32	41
13–24	5	12 (4)	1	3	15 (4)	18 (4)
25–36	5 (1)	2		4	3 (1)	7 (1)
37–48		1	1 (1)		2 (1)	2 (1)
49–60		1 (1)			1 (1)	1 (1)
>60	1	1			2	2
Total	28 (1)	49 (5)	3 (1)	18	62 (7)	80 (7)

A, adenocarcinoma; S, squamous cell carcinoma

* Numbers in parentheses indicate number of patients still alive January 1986.

† Under 30 days; "operative mortality," as defined in this study.

aortogastric fistula caused one death; neither an esophagogram on the 7th postoperative day nor autopsy showed any evidence of an anastomotic leakage in that patient. One patient died suddenly on the 7th postoperative day, due to mucous plug in the trachea. A sudden cardiac event on the 30th postoperative day was responsible for the death of one patient. The patient who sustained an azygos-vein injury died on the 12th postoperative day from multiple organ system failure. The remaining 4 patients died of adult respiratory distress syndrome, ranging from 6th to 22nd p.o. day.

Late mortality: All patients were followed up until their deaths or to January 1986. Thus, follow up is 100%. Mean survival of the entire group (71 patients), excluding the operative deaths, was 16 months, and median survival was 11 months. Among 46 patients followed up for a minimum of 5 years, only 2 survived more than 5 years (one for 79 months, one for 96 months). Both patients had squamous cell carcinoma. Among 64 patients followed up for a minimum of 3 years, 11 survived more than 3 years. A total of 41 patients died in less than 12 months. Seven patients were still alive, with or without the disease, at January 1986. The longest survival time among these 7 is 54 months. Four of the 7 were operated on within the last 2 years of the study (Table 5).

Discussion

Carcinoma of the esophagus remains one of the most challenging surgical problems. There has been little change in the five-year survival rate for the past several decades (1). There are two main reasons for this grave prognosis (2–4): delay in diagnosis, because patients may remain symptom-free for a long time; and lack of effective treatment, except for surgical treatment, which is palliative at best. A mass screening procedure using brush cytology techniques, such as the one developed in China (14), is certainly an effective measure in places where the incidence of carcinoma of the esophagus is high. A trial of this screening procedure was performed at the Bronx VA Medical Center with low yield, although the test was conducted with a group of patients at high risk (15). The cost-benefit effectiveness of this type of screening in the United States remains to be proven.

Various modalities of preoperative and postoperative adjunctive treatments have been tried, with little success (16–21). Recently, preoperative chemotherapy with cisplatin as a main agent has been reported; initial results were promising (22). A preliminary protocol for combined preoperative chemotherapy and radiotherapy was established in our institution in 1982 and a total of 11 patients were included in this study by the end of December 1984. Six of these patients were operated on; there was one long-term survivor (alive at 36 months with no evidence of tumor). The other 5 patients were not operated on, either by their choice or for a variety of medical reasons. The chemotherapy utilized in the protocol is a combination of cisplatin and moderate-dose methotrexate with citrovorem-factor rescue, and bleomycin. Bleomycin was omitted in some patients because of concern over pulmonary complications. Intraoperative PO_2 must be carefully regulated when bleomycin is used. Chemotherapy is followed by a course of radiotherapy for 5 days, 200r twice a day, for a total dose of 2,000r, felt to be biologically equivalent to 3,000r. Surgery is performed immediately after completion of the entire treatment, provided the white blood cell count is above 3,000 with no downward trend.

The most remarkable effect of this treatment was on the tumor itself. The mucosal surface quite often showed almost complete sloughing of the tumor. The deeper layer of the tumor and metastatic nodes seemed to be less affected. The long-term prognosis with this adjunctive treatment remains to be seen.

CT scan of the chest, including the upper abdomen, provides useful information for evaluation of both local extent of the disease, and some conditions previously undetectable. For example, unsuspected pleural and lung metastases were found by CT scan, and these patients were treated without surgery.

Another important point of preoperative evaluation and care is the nutritional status of these patients. The majority of the patients were markedly dehydrated and malnourished. Sufficient hydration is mandatory prior to surgery and may be more important than caloric intake per se. These patients are also quite often anemic, and transfusion may be needed. One pint of blood transfusion per 10 lb of weight loss is a good general guide line (23). Extensive efforts should be made to provide sufficient caloric intake by gastrointestinal tract.

At present, surgical management via esophagogastrectomy with esophagogastrostomy as a one-stage procedure is considered the most effective treatment for carcinoma of the esophagus. Although this procedure was first performed more than forty years ago (24), it is still one of the most challenging of surgical procedures. The operative mortality and morbidity are fairly high, mainly due to the high incidence of anastomotic leakage (9, 12). It is essential to maintain low morbidity and mortality if this procedure is to be effective palliation. Our present series showed a very low rate of anastomotic leakage, 3.7% (3 of 80), with only one case of fatal leakage, one of the two cases of leakage from the intrathoracic anastomosis in 73 patients. In this case, some difficulty was encountered during the anastomosis due to limited exposure (left thoracoabdominal incision). The outcome might have been different if a right thoracotomy had been used. The other case of intrathoracic anastomotic leakage was due to erosion of a chest tube into the gastric stump closure line and resolved immediately following withdrawal of the tube. One case of leakage from the anastomosis in the neck occurred following esophagectomy without thoracotomy. The amount of leakage was small, and the leak healed without any specific treatment.

Our anastomotic techniques are standard ones as described in the literature (25, 26) including the use of the intraluminal circular staple (27). No special technique was used. No special technical dexterity can be claimed, because the resident staff performed all surgery under direct supervision of one of the authors. We strongly believe that careful observation of fundamental surgical principles is a key element for successful surgery. Gentle handling of the tissues, preservation of the blood supply, avoiding injury to the proximal esophageal stump, and covering the anastomotic suture line with serosa are a few points that influence the outcome of the surgery. It is very important to cover the suture line with serosa, preferably with a fundoplasty, for this gives extra protection to the suture line as well as preventing gastric reflux (28, 29).

Though our operative mortality rate was at an acceptable level, it could have been lower. When the cause of death was analyzed (Table 4), technical factors were shown to be responsible in 3 patients. One was due to leakage from the anastomosis, as mentioned above. The second was due to azygos vein injury. The third was a case of aortogastric fistula, resulting in a massive upper gastrointestinal hemorrhage on the 10th postoperative day. An autopsy showed definite fistula from the inferior aspect of the arch of aorta to the anastomotic suture line, but failed to show an exact cause of the fistula. Neither microabscess nor any other findings suggestive of leakage were noted. No residual tumor was seen either. One possible cause of the fistula is an aortic injury produced by a stiff, sharp end of the suture material. The anastomosis was performed with 3-0 polypropelene and was next to the aortic arch.

Five patients died of respiratory problems. One was due to a mucous plug in the trachea; this could and should have been avoided. Four died of ARDS. Two of three who died from this syndrome in 1982 received a combination of preoperative chemotherapy and radiotherapy. These cases occurred at the very beginning of this protocol, and the pulmonary problems associated with bleomycin were not fully appreciated. This has been corrected and no further deaths have occurred due to the same problem.

No postoperative deaths occurred in 36 consecutive cases between 1973 and the beginning of 1980 (Table 6). In this period, there was only one

TABLE 6
Mortality Trends

Year	No. of patients	Deaths
1970–1974	18	3
1975–1979	29	0
1980–1984	33	6
Total	80	9

case of suture line leakage, involving minimal leakage from the cervical anastomosis. The unusually high number of deaths due to respiratory failure in 1982 is ascribable partially to decreased resistance to infection following the protocol treatment, and particularly to oxygen toxicity associated with bleomycin.

Several different approaches, depending on the individual attending surgeon's choice, were utilized in this series. The two most commonly used approaches were a left thoracoabdominal incision and a combination of a right thoracotomy and midline abdominal incision. A major advantage of the latter is the good exposure at the time of anastomosis (26). A good anastomosis, which quite often is performed near the apex of the thorax, is key to successful surgery. It is very difficult, if not impossible, to perform an anastomosis high in the pleural cavity through a left thoraco-abdominal incision. A combination of the right thoracotomy and midline abdominal incision provides excellent exposure and was used almost exclusively in the last several years of the study period. Left thoraco-abdominal incision is reserved for patients with cancer of the cardia when a low anastomosis can be anticipated. Esophagectomy without thoracotomy (30, 31) was performed in highly selected cases only.

For an examination of the anastomosis, we preferred to use a cine-esophagogram rather than a standard esophagogram. The advantages of this technique are (a) superior visualization of flow of the contrast (either gastrographin or very thin barium), (b) better evaluation of the dynamic status of the stomach, and (c) repeated opportunities for reviewing the studies. Spot films can be taken as needed.

The poor long-term survival in this series is similar to that reported previously (3–5). Only 2 patients survived more than 5 years; median survival was only 11 months. Clearly, in most instances the surgical procedure is not curative, but only a palliative measure. We hope that earlier detection of the disease and the development of effective adjunctive treatment will improve long-term results; at that juncture surgical treatment will become a truly curative measure.

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Recovery of Pancreatic Function after Distal Resection for Chronic Pancreatitis: Regeneration or Merely Functional Amelioration?

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Abstract

Exocrine and endocrine pancreatic function before and after distal resection has been studied in 25 patients with chronic pancreatitis. The results of the tubeless, secretin-pancreozymin, and Lundh tests demonstrated well-preserved pancreatic secretions and a significant recovery of exocrine function despite about 60% loss of pancreatic mass. Glucose tolerance was frequently decreased. Enzyme changes were similar to those seen after treatment with cholecystokinin-pancreozymin (CCK-PZ). Recovery of exocrine pancreatic function after distal resection was attributed to a real regeneration of acinar cells, possibly triggered by increased release of endogenous CCK-PZ.

Chronic pancreatitis is generally a progressive disease (1) but if the cause (for example, alcohol consumption) has been eliminated, some functional recovery could occur (2). Significant recovery of exocrine pancreatic function was observed in a preliminary study of pancreatic secretion following distal resection in humans (3).

This is a report of a detailed analysis of the functional data of an enlarged group of patients with distal resection for chronic pancreatitis. Our data suggest not only clinical amelioration, that is, decreased frequency of relapses, but also a real regeneration of acinar cells.

Patients and Methods

We have examined the pancreatic function of 25 patients with chronic pancreatitis after distal resection of an average of 56% ± 3.5% (range, 40%–95%) of the pancreas. The age of the 7 women and 18 men was 39.2 ± 1.9 years (range, 24–57 years). Indications for the operation were stones, strictures, or severe morphologic alterations in the distal part of the pancreas demonstrated by endoscopic pancreatogram associated with typical pain or progressive functional damage. In 16 patients, alcohol consumption resulted in calcifying chronic pancreatitis, in 2 patients intraductal carcinoma was found, and in 7 patients scarring after healing of pseudocysts caused obstructive chronic pancreatitis.

Pancreatic function was studied by secretin-pancreozymin test (4) and/or Lundh test (5), by Lipiodol test (6), by fat loading in patients with manifest steatorrhea (7), and by glucose-loading and starch tolerance tests (8) in patients without manifest diabetes 15 ± 2.8 months (3–48 months) after surgery.

In 11 patients before operation and in 15 patients 24 ± 4.6 months (7 – 57 months) after surgery, a second Lundh test and another study of glucose tolerance were done. Seven patients had all three tests. Pancreatic function was checked

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TABLE 1

Results of Secretin-Pancreozymin Test and Lundh Test after Distal Resection of the Pancreas

			Amylase		Trypsin		Lipase	
	Volume (ml/min)	Max. HCO_3 concentration (mM/liter)	Activity (U/ml)	Output (U/min)	Activity mU/ml	Output (U/min)	Activity (U/ml)	Output (U/min)
Secretin-pancreozymin test (*n* = 11)								
Lower limit of normal values	143 ml/60	82	72	17102 U/60	160	47 U/60	24	4535 U/60
After operation	178.4* ± 19.4	77.0 ± 10.3	102.0 ± 25.3	20665.3 ± 5794.0	301.0 ± 64.1	63.0 ± 18.1	59.7 ± 14.0	10719.6 ± 3073.9
Lundh test (*n* = 25)								
Lower limit of normal values	131 ml/30	—	39	8661 U/30	219	45 U/30	41	7880 U/30
After operation	226.2 ± 15.8		49.8 ± 6.6	10720.0 ± 1680.6	245.3 ± 53.2	54.9 ± 11.7	27.9 ± 3.5	5945.7 ± 971.9

* $\bar{x}$ ± SEM.

at least 3 months after the last relapse of pancreatitis to demonstrate a stable phase of the disease. Although we encouraged the participants to eliminate all alcohol consumption, total abstinence was not always achieved during the long observation period.

Results

Exocrine pancreatic function was well preserved in spite of the significant loss of pancreatic mass and obvious histologic signs of chronic pancreatitis (Tables 1, 2). Manifest steatorrhea with an average of fat loss of 43.7% ± 13.3% (7.7%–89.6%) occurred in only 7 patients.

Indeed, in the 11 patients examined before and after operation, the Lundh test showed a 25% overall increase in enzyme secretion (Fig. 1). Trypsin and lipase increases were more pronounced than increases in amylase. During the late postoperative period, enzyme output increases were parallel but not significant (Fig. 2).

Glucose tolerance significantly decreased in 4 cases among the 11 pre- and postoperatively examined patients (Table 3). No improvement of glucose tolerance after resection was noted in these patients and in others studied under different protocols (data not shown). However, deterioration of diabetes mellitus was not frequently accompanied by a decrease in enzyme secretion. Indeed, overall increases in enzyme secretion were slightly higher in patients with chronic calcifying pancreatitis (+32.9%) than in patients with chronic obstructive pancreatitis (+10.3%). Significant deterioration of glucose tolerance was more frequently demonstrated in patients with calcifying pancreatitis (4 versus 1).

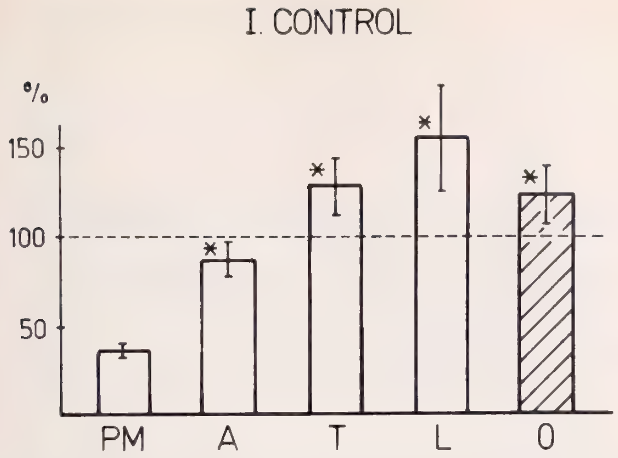
Clinical relapse, proved by pain and elevated blood or urinary amylase levels, occurred in the same proportion of the patients with calcifying (5 cases) and noncalcifying (3 cases) pancreatitis after resection. The attacks were provoked by insignificant intake of alcohol with or without heavy meals.

TABLE 2

Results of Indirect Pancreatic Function Tests after Distal Resection

			Glucose tolerance			
	Lipiodol test (*n* = 22)	Amylase tolerance test (*n* = 13)	Normal	Latent DM	Manifest DM	Insulin-requiring DM
Limits of normal values	>2.4 mM/24 hr	<70%				
After operation	1.71* ± 0.24	157.0 ± 45.1	6	11	3	5

DM, diabetes mellitus.
* $\bar{x}$ ± SEM.



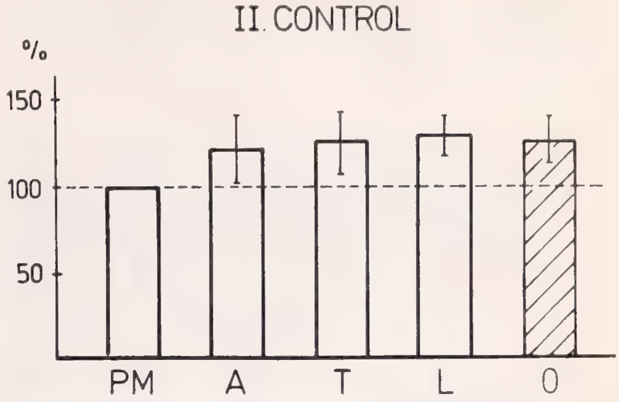


Fig. 1. **Left** Percent changes in pancreatic mass (PM), amylase (A), trypsin (T), lipase (L), and overall enzyme secretion (O) estimated by Lundh test before and after distal resection of pancreas. Preoperative values are taken as 100%. Overall enzyme changes were calculated from cumulative percent values of outputs of the three measured enzymes (the sum of % changes divided by 3). Values are mean ± SE of 11 patients. Significant differences from presumed values relevant to remaining pancreatic mass (Wilcoxon test, $p < 0.05$) are indicated by *.

Fig. 2. **Right** Percent changes in Lundh test values 24 ± 4.6 months after operation. Results of postoperative control group I were taken as 100%. Overall changes were calculated as in Fig. 1. Values are mean ± SE of 15 patients.

Discussion

Direct and tubeless pancreatic function tests demonstrated surprisingly well-preserved exocrine pancreatic function in our patients with calcifying or obstructive chronic pancreatitis in spite of the 60% loss of pancreatic mass. The extent of resection was dictated by the extent of damage to the duct as determined (9) by endoscopic pancreatography. Serial histologic samples indicated that relatively intact parts of the pancreas positioned near the resection line were also removed.

Amelioration of exocrine secretion after operation could be the consequence of healing of an acute pancreatitis if resection of damaged pancreatic mass eliminated the lesion causing persistent inflammation. In acute pancreatitis, however, decrease in glucose tolerance is typical (10), but after resolution of inflammation, endocrine recovery and not deterioration (11) is to be expected.

TABLE 3

Glucose Tolerance before and after Distal Resection of Pancreas

	Glucose tolerance			
	Normal	Latent DM	Manifest DM	Insulin-requiring DM
Before resection	2	7	1	1
Control group I after resection	2	4	1	4

DM, diabetes mellitus.

Diminished glucose tolerance in contrast to the restoration of exocrine function indicates that the resected part of the pancreas was endocrinologically active. The marked decrease in glucose tolerance occurring in calcifying cases presents a real problem in major distal resections (12).

Enzyme concentrations of duodenal secretion after resection were similar to those seen after prolonged CCK-PZ treatment for chronic pancreatitis in humans (5). Diminished acinar cell mass in severe chronic pancreatitis was accompanied by elevated basal and postprandial CCK-PZ plasma levels (13). Increased endogenous CCK-PZ release stimulated by diminished intraduodenal trypsin activity (14) appears to be involved via a feedback mechanism that may play a role in the secretory changes provoked by pancreatic resection. Regeneration of acinar cells, but not of insular parenchyma, may explain divergent changes in exocrine and endocrine function. In animal experiments, too (15), CCK-PZ fails to have any trophic effect on the islets.

Trivial alcohol consumption resulted in relapse of disease and further deterioration of pancreatic function. In fact, after CCK-PZ treatment in humans (5, 16) and rats (17), susceptibility of the pancreas to alcohol appears to be increased. Total abstinence is an absolute prerequisite for functional recovery after resection.

In conclusion, not only improvement of pancreatic function but also real regeneration of the pancreas probably triggered by increased endogenous CCK-PZ release occurs after distal resection of the gland for chronic pancreatitis. Inhibition of this pancreatic regeneration results from alcohol consumption (2), an effect more pronounced after resection than before.

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Medical Information

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Early Gastric Carcinoma Diagnoses in Japan: Radiologic, Endoscopic, and Pathologic Alert

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A journalistic medical curiosity took me to visit Tokyo to see for myself how the Japanese can obtain the fantastic results of 90% to 100% five-year survival rates for patients with early gastric carcinoma. In the United States, the five-year survival rate for gastric carcinoma has been 10%, lately improved to 13%, according to the American Cancer Society. In my previous practice of gastroenterology and my current experience as a pathologist, I have developed a pessimistic outlook on the disease, having followed only very few patients who survived for five years after surgery for the disease; all have succumbed thereafter. I traveled to discover the Japanese secret, I found it, and I want to share it with you.

A Japanese-American pathologist and a radiologist made the necessary contacts in Tokyo with a prominent pathologist, Dr. K. Nakamura, and a highly respected professor of medicine and a radiologist, Dr. Shirakabe, and they were extremely generous with their time, knowledge, and teaching material.

In 1960 they organized the Japanese Society for Detection of Early Gastric Carcinoma. They started by defining their aim, which was to detect in the general population the asymptomatic early gastric carcinomas (EGC). They defined as an early gastric carcinoma "the cancer whose extent is within the confines of the mucosa or utmost within the submucosal layer"; cancers infiltrating beyond the submucosa are already advanced.

Typology. The Japanese Gastroenterological Society (1962) has classified the EGC macroscopically into 3 types (Fig.): a protruding type (I); a superficial type (II), subdivided into elevated (IIa), flat (IIb), and depressed (IIc); and an excavated type (III). Applying this classification, radiologists, endoscopists, surgeons, and pathologists can understand each other, and as the story evolves, you will see that these classes have diagnostic and pathological connotations. An EGC can be a mixed type, in any combination; for example, flat with an area of depression—IIb and IIc.

Screening. To find the early lesions, they screened the adult population. Nearly 90% of the mass screening is conducted by mobile units manned by radiology technicians, who can screen 50 to 60 persons in one morning, obtaining 6 standard exposures using an image intensifier to decrease the radiation exposure, using a roll of film 70–100 mm in width. The x-ray films are examined by two specialists independently. If any suspicious lesion is found, the patient is recalled for a double-contrast upper gastrointestinal series, and if the radiological lesion is confirmed, the patient is scheduled for endoscopy, and biopsy, if a lesion is found. If the biopsy is positive for carcinoma, a partial gastrectomy is advised. Of 100 cases screened by the mobile units, 15 go for detailed double-contrast upper GI series, and of these, 25% go for endoscopy examination (4 patients of every 100).

India Ink to Identify Safe Resection Levels. I have been told by a surgeon that lately the gastroscopists inject India ink into the most proximal normal gastric mucosa so that the surgeon will know a safe level for resection and anastomosis, because these early carcinomas are not detectable on palpation by the surgeon. The surgeon may decide to remove different topograph-

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ical groups of lymph nodes, depending on the location, size, and depth of the tumor.

Pathologic Procedures. The pathologist opens the stomach along the greater curvature and pins it to a wooden board. The gastric mucosa is described, photographed, and fixed in a tank of formalin; the board is placed sideways with a heavy metal rim to keep it submerged. After 2 to 5 days of formalin fixation, the stomach is washed in running water for 24 hours. The fixed stomach is examined carefully and photographed again. My Japanese friends played a game with me by showing me pictures of the actual stomach and asking me to find the lesion. I learned to seek out an interruption of a fold, a depressed area with converging folds, small erosions in the antrum or granular mucosal surface. When I learned how to find the very small lesions of the EGC, we both were very proud, they as teachers and I as a student. I was exposed to the same zealous teaching by the radiologists and endoscopists.

The fixed and washed stomach is put on a paper with several carbon copies, the margins are drawn, including the holes made by the nails used to pin the stomach. The stomach is cut in its entirety, starting with an equatorial line in the middle of the lesser curvature, and using parallel cuts approximately every 15 mm and transverse cuts every 40 mm, ending up with approximately 48 blocks. Every line and rectangle is numbered: by convention the pylorus is always to the left, the upper part is the anterior surface, and the lower the posterior surface. The lesion is drawn on the paper on the corresponding lines and rectangles, the lesion type is labeled (IIb and IIa, for example, if that is the case), and a note is added on whether they see gross involvement only of the mucosa (*m*) or of the submucosa (*sm*) as well. The final extent of involvement is established when the histologic sections are returned.

By such extensive pathologic study they arrived at interesting discoveries. The 10% of multiple gastric carcinomas found on radiologic and endoscopic examination becomes 15% after the pathologic examination.

Fundic Mucosal Changes in the Elderly. In a young person's stomach, the antral, fundic, and cardiac mucosa, respectively line the approximate anatomic areas designated as antrum, fundus or body, and cardia. The Japanese workers observed that in elderly people, the HCl pepsin-secreting fundic mucosa regresses and is replaced by antral mucosa. In elderly people, the fundic mucosa can be limited to a small area in the vicinity of the greater curvature. This is a natural gerontologic process and does not have a premalignant connotation.

They do find a sequential correlation of gastritis with intestinal metaplasia and gastric carcinoma. Most of the gastric carcinomas arising in the antral mucosa are well-differentiated adenocarcinomas, forming glands or tubules. These tumors have a tendency to invade lymphatics and venules and metastasize to the liver via the portal circulation. By contrast, almost all of the carcinomas arising in the fundic mucosa are poorly differentiated, most of them signet-ring cell type, with a tendency toward diffuse invasion of the stomach (linitis plastica), the peritoneum, pelvic organs (Krukenberg tumor). Most of the fundic undifferentiated carcinomas are IIc or III (depressed or excavated), and are seen in younger patients. The type I and IIa (polypoid, elevated) lesions are frequently well-differentiated and seen in the antral mucosa of elderly patients.

Mucosal Carcinomas: 100% Five-Year Survival. The prognosis of the patients with gastric carcinoma depends on the extent and depth of invasion and the status of the regional lymph nodes. The Japanese team has seen mucosal carcinomas of 9–10 cm, some of them without lymph node involvement. The team members are very proud of their very small, 5–10 mm mucosal carcinomas, none with lymph node involvement.

Those early carcinomas limited to the mucosa had 100% five-year survival and 96% ten-year survival; those also involving the submucosa had 97.7% five-year survival and 93% ten-year survival. When the cancer is limited to the mucosa, the Japanese found 4% with lymph node involvement; those extending to the submucosa had 18.9% lymph node involvement. The advanced cancers involving muscularis propria had 57.3% lymph node involvement.

By mass screening they found 4% of unresectable carcinomas with 0% cure rate, 49% resectable with a 50% cure rate, and 47% early gastric carcinomas with a 90% cure rate. In the mass screening, they had an overall 72% survival, compared to 40% survival in the clinic patients.

The cost per early gastric carcinoma in Japan is $76,000, and in the Tokyo Cancer Center it is $23,000. The discussion now in the Society is of the economic burden of the mass screening; they will, for the time being, shift screening to every other year instead of yearly. The cost is taken up by the Japanese budget, except when an industrial complex or corporation decides to check its employees.

By now, every one of the Japanese cancer centers has identified a thousand or more early gastric cancers, but the Early Gastric Cancer Society keeps meeting with the same enthusiasm as it did initially decades ago, once a month presenting new studies and interesting cases. Once a week, surgeons, radiologists, and endoscopists meet in the pathology department where the stomachs are going to be sectioned to compare their findings with the final diagnosis.

Need for Biopsy at a Curable Stage. I have shown the double-contrast upper GI x-rays that they so generously provided me for teaching purposes, to my radiologist friends in the United States and they find them "exquisitely clear." The EGC type IIc usually arising in fundic mucosa is the easiest to recognize radiologically; the depression is surrounded by ill-defined concave borders with converging folds.

The endoscopist finds a similar picture of a depression in an area of converging folds. In these cases, the biopsies should also be taken from the depression. The malignant lesions of 1 cm or less in the antrum, usually IIb-IIa or any combination, and usually well-differentiated, are not detectable by radiology since there are no folds to point to the lesion. The endoscopists may only perceive a darker red area. The American endoscopists may not be aware of the significance of these changes and therefore may not biopsy the lesions when they are in a curable stage.

"Malignant Cycle" Entity—Differentiating Carcinoma and Peptic Ulceration. I would also like to emphasize an entity called malignant cycle. A IIc and III lesion is a depressed superficial carcinoma with central peptic ulceration. The peptic ulceration can heal and the lesion reverse to a IIc. With a double-contrast x-ray film, the lesion is seen as a depressed area surrounded by concave ill-defined borders and convergent folds with a central ulceration. The danger in our country is that the entity will be ignored and interpreted as only a peptic ulceration that healed under medical treatment. The malignant cycle is usually an undifferentiated IIc in fundic mucosa in a younger person.

Histologic Groups and the Uses of Endoscopy and Biopsy. Pathologists have classified the gastric biopsies in 5 histologic groups. Groups I–II and V are well-defined; I is normal gastric mucosa, II is found in regenerated epithelium taken from the borders of an ulcer or erosion and V is carcinoma. Group III lesions are called intermediate. They appear grossly as a slightly elevated, well-delimited area, no larger than 2 cm in diameter, with a uniform, granular surface of the same color as or slightly paler than the gastric mucosa. A biopsy taken from this lesion shows evenly spaced, regular, crowded glands lined by cuboidal or low cylindrical cells with uniform basal nuclei. A few stomachs with such lesions were removed in the early years of the program when there was not enough experience with the entity. After that, they followed 30 cases for about 10 years; the lesions did not change size and histologically they remained the same. If the lesion becomes larger than 2 cm and the surface shows an area of irregular granules, a well-differentiated adenocarcinoma may be present in that corner, as Dr. Nakamura showed me in one case. In a conversation over lunch with an endoscopist, he told me that they learned to resect the III intermediate lesion endoscopically by pulling and cutting it off. The group IV lesions are also flat, elevated, but with irregular granular surface. Histologically, the glands are of different size, irregular in shape and covered by taller cells with plump nuclei and prominent eosinophilic nucleoli. A biopsy taken from such a lesion can be highly suspicious for carcinoma. They follow these cases by endoscopy and repeat biopsies, and in most of the cases they are confirmed as carcinoma. If the patient refuses repeat endoscopy, he has to be operated on.

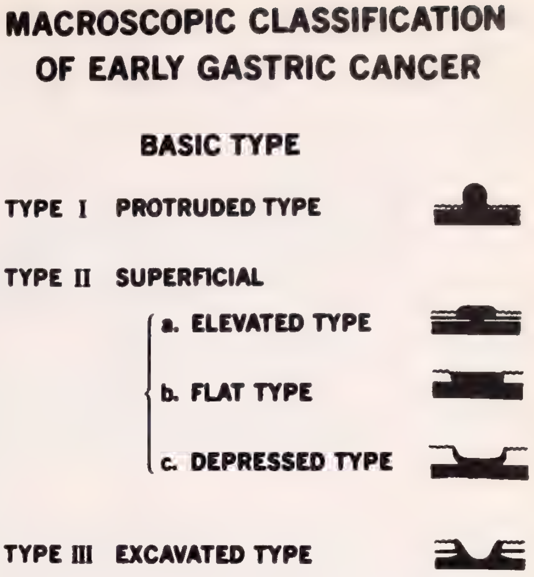

Fig. Macroscopic classification of early gastric carcinomas developed by the Japanese Gastroenterologic Society.

What We Can Learn. In 1960, when the Japanese medical community decided to organize itself to combat their nation's most frequent carcinoma, the incidence was 70 gastric cancers per 100,000 population per year; this has now fallen to about 50 per 100,000. They attribute the improvement to the early gastric cancer diagnosis campaign as well as to changing dietary habits, which may also be the cause of the rise in the number of colonic carcinomas.

In the United States we have 9.1 gastric cancers per 100,000 population, and that number does not warrant a similar campaign to find the asymptomatic early gastric carcinomas. The low number of cases is in part a consolation, but unhappily they will have a fatal outcome.

My aim is to communicate my experience to radiologists, endoscopists, and pathologists to remind them of the entity. Upper gastrointestinal series and endoscopies are done for many reasons; among the patients so studied may well be someone with early gastric carcinoma. Dr. Nakamura and others have estimated that it takes 10 years for such an early cancer to become an advanced, symptomatic gastric carcinoma as we usually see it.

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I want to express my most sincere gratitude to those who so generously gave me their time, knowledge and friendship: Dr. Hikoo Shirakabe, Dr. Kyoichi Nakamura, Dr. Heizaburo Ichikawa, Dr. Teruyuki Hirota, Dr. Yo Kato—and many more.

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What Has Cyclic AMP to Do with Gastric Acid Secretion?

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The conclusions drawn from current fashionable studies on isolated gastric glands and parietal cells put the whole-animal gastrointestinal physiologist into a mood of skepticism and uncertainty. The main cause of disquiet is the air of certainty surrounding the notion that cyclic adenosine monophosphate (cyclic AMP) mediates gastric acid secretion and that aminopyrine retention is a true measure of acid secretion. An example of this is a question on a National Board examination a few years ago in which students were expected to agree that the action of gastrin on the parietal cell is mediated by cyclic AMP.

Many hormones and chemical agents are known to increase cyclic AMP levels within cells. Of those that have been tried, all except the xanthines (1) depress gastrin-stimulated acid secretion in conscious dogs (2–6), and adrenergic agents increase cholinergically stimulated acid secretion from innervated pouches (1). One would infer from this that the action of the xanthines and adrenergics on acid secretion under the special circumstances noted above is by a mechanism that does not involve cyclic AMP.

Shortly after the discovery of the second messenger role of cyclic AMP, there was a great scurry to implicate it in gastric acid secretion. In 1976 Jacobson and Thompson (7) concluded that there was no convincing evidence for or against an obligatory role for cyclic AMP in gastric acid secretion. Histamine and pentagastrin have been claimed to increase the activity of mucosal cell membrane adenyl cyclase in dogs (8). Histamine was found to increase fundic but not antral mucosal enzyme activity in rabbit mucosal homogenates. Prostaglandins increase both, the antral adenyl cyclase more than the fundic, in cell-free mucosal homogenates from dogs, but inhibit acid secretion (9). Prostaglandin action was found to be resistant to the H_2 blocker metiamide, to which histamine and fluoride activation was sensitive. It has been stated that theophylline increases mucosal cyclic AMP in dogs but does not stimulate acid secretion (11). Pentagastrin did not increase adenyl cyclase activity in fundic mucosal homogenates from the animals named above but did stimulate acid secretion. No increase in adenyl cyclase activity was observed with histamine. The effect of histamine on acid secretion was potentiated by xanthines in dogs, but the effect of pentagastrin was not potentiated in dogs or humans. In dogs and humans (12) neither pentagastrin, betazole, nor histamine was found to increase adenyl cyclase or cyclic AMP in fundic mucosa. There is a similar scatter of contradictory evidence for intact rats and guinea pigs. Every possible permutation or combination of high and low cyclic AMP, adenyl cyclase activity, and acid secretion has been reported (13). Some have found that histamine increases adenyl cyclase activity in rat gastric mucosa and others not (14), and in at least one paper it was reported that exogenous cyclic AMP depressed gastric acid secretion in both dogs and humans (15). In 1973 Mao et al. (16) showed that although both intraarterial and intravenous histamine and pentagastrin increased acid secretion in dogs under chloralose, neither increased mucosal cyclic AMP; and papaverine, which increased cyclic AMP, did not stimulate secretion. These authors (16) used dibutyryl cyclic AMP, which, given

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intra-arterially, has been said to cause acid secretion in rats and to provide indirect evidence for acid secretion in isolated parietal cells. It did not cause acid secretion. In 1973 Bieck et al. (17) claimed that the cyclic AMP in gastric juice in humans correlates directly with the acid output in response to both pentagastrin and histamine.

The argument has been advanced that the various inhibitory and inactive agents mentioned above increase cyclic AMP or activate adenyl cyclase in all of the gastric mucosal cells, but lower histamine-activated adenylate cyclase in the parietal cells (18), and that only the xanthines increase it in both. So far this contention has not been tested thoroughly. It seems clear that the increase in cyclic AMP after treatment with histamine is confined to parietal cells (19), but it is not clear that the agents that increase mucosal cyclic AMP and inhibit acid secretion actually depress parietal cell cyclic AMP. In 1984 Shepp and Ruoff (20) claimed that glucagon, which is known to depress acid secretion (3), does increase cyclic AMP in isolated parietal cells but does not interfere with the action of histamine. They concluded that glucagon activation of adenylate cyclase does not stimulate acid secretion and that the inhibition seen in vivo is not mediated by cyclic AMP, and they inferred, as have others mentioned above, two separate adenyl cyclase systems. Prostaglandin E_2 has been studied in isolated parietal cells, but even it does not diminish cyclic AMP levels; in fact, it raises them, but not as much as does histamine, and it decreases the histamine-induced elevation (21).

Measuring H^+ Secretion

The recent and very popular techniques using isolated parietal cells avoid the difficulty of separating out incidental changes in nonparietal cells, but a new difficulty is introduced in that it is impossible to measure H^+ secretion directly, and the indirect methods give only a qualitative indication of acid secretion. The first method used was oxygen consumption, which is both nonspecific and indirect (22). It is usually justified by claiming a close dependence of acid secretion on O_2 consumption, but McQuarrie and Vennes (23) have stated that in the maximally secreting stomach fully one-third of the energy for acid secretion is anaerobically derived. Furthermore, it does not seem ever to have been determined that gastric secretagogues do not increase O_2 consumption in other cells. It is inferred by comparing enriched with unenriched suspensions that responses to secretagogues are due almost entirely to the parietal cells (22).

The other method for measuring H^+ secretion is with aminopyrine (24). This agent distributes itself throughout the body fluid. It has a pK of 5.0; at lower pH values most of it will be ionized and will be unable to cross cell membranes. It is well secreted in gastric juice when it is acid, so much so that it has been used to measure gastric blood flow. The inside of the parietal cell is not acid during secretion, but the intracellular canaliculi are. Berglindh et al. (25) have contended that not all of these open to the exterior, and thus acid and aminopyrine will be secreted into them and become entrapped. If radiolabeled aminopyrine is used in isolated cell suspensions it can be counted after washing the cells. Aminopyrine does not accumulate in the other mucosal cells that may be in the suspension. Obviously, such a method cannot be quantitative. Acid indicator dyes have been used to confirm that the sequestered residues do contain acid (24). Hundreds of studies have been conducted with this isolated parietal cell system and, amazingly, practically all are based on aminopyrine uptake. No doubt seems to have been cast on the method. Nor, it seems, have attempts to test its validity been published. This must be unique in experimental physiology.

What has been found? Histamine increases cellular cyclic AMP and aminopyrine uptake (24). The doses used are large, but the effect is blocked by H_1 and H_2 antagonists. The H_2 antagonist (cimetidine) was much the more potent (26). To obtain good effects, xanthines—which inhibit phosphodiesterase—were used. These greatly increased the ability of histamine to increase cyclic AMP, and dibutyryl cyclic AMP itself promoted aminopyrine uptake, but the dose required, 10^{-3} M, was very large. Curiously, pentagastrin, which is much more potent than histamine as an acid stimulus, neither promoted O_2 uptake and aminopyrine retention nor increased cyclic AMP (27). Cholinomimetics caused only a transient uptake of aminopyrine and no increase in cyclic AMP or O_2 consumption. Soll has claimed that both increase the action of histamine on O_2 consumption but do not increase cyclic AMP accumulation (28). One of the best stimulants of aminopyrine uptake is aminopyrine itself. Perhaps those sequestered canaliculi are an artifact caused by aminopyrine (25).

Difficulties in Interpretation

A serious difficulty in interpreting this work is that several inhibitors of gastric secretion—prostaglandin E_2 (29), glucagon (20), and secretin (29)—have been found to increase cyclic AMP in fundic cell preparations from dogs and guinea pigs. In addition, secretin has been found to activate adenyl cyclase in rat parietal cells (29). Agents that depress carbonic anhydrase activity depress histamine-stimulated acid secretion, but were found not to interfere with aminopyrine uptake in isolated rabbit parietal cells (31). In only one study has acid secretion actually been measured and correlated with the cyclic AMP content of parietal cells (32). This was in pig gastric mucosa. Histamine increased acid secretion to a plateau and cyclic AMP did increase about 5–10 min before secretion, but by the time of full acid secretion the cyclic AMP had declined again. This had been noted earlier by Bieck et al. (17) in studies of dog gastric juice. After isobutylmethylxanthine, cyclic AMP remained high and so did acid secretion. This agent increased cyclic AMP after histamine but did not increase acid secretion further (32).

Studies on isolated gastric glands have given almost identical results and have resolved none of the puzzle. Gastrin does not act at all; the action of carbachol is momentary and its stimulation of O_2 consumption was not augmented by aminophylline but was augmented by dibutyryl cyclic AMP (33).

What Conclusions Are Justified?

What is to be concluded from this? Is cyclic AMP an obligatory intermediate for acid secretion no matter how the secretion is stimulated? One cannot tell. In isolated cells it seems as if it is not, but the preparation of the tissue may have destroyed its receptors. Is cyclic AMP an intermediate for histamine-stimulated secretion? Again, it may be. Are sustained levels needed, or is cyclic AMP simply a trigger? I think the evidence is better for the latter, but the action of histamine in stimulating cyclic AMP production and acid secretion may have no sequential causal relationship at all. It is true that H_2 blockers block both, and some have maintained that H_1 blockers do so as well on isolated cells with aminopyrine accumulation as an index of acid production (26, 27). Xanthines increase cyclic AMP levels and aminopyrine accumulation in isolated cells, but xanthines have been claimed by some not to stimulate acid secretion in dogs or humans or to potentiate the action of pentagastrin (11) and by others not to cause aminopyrine accumulation in cells on their own (34).

Are there circumstances under which parietal cell cyclic AMP increases and acid does not? There seem to be; prostaglandins (30, 29), glucagon (20), papaverine (16), secretin (19), VIP (35) do this but depress gastric acid secretion. Many other agents stimulate adenyl cyclase activity in most cells, but their actions on acid secretion in intact animals and cyclic AMP accumulation on isolated cells have not been compared; however, from what is known now one cannot say that every increase in cyclic AMP in the parietal cell starts acid secretion. Can one have acid secretion without an elevation in cyclic AMP? Again, it is hard to say; pentagastrin does not stimulate either, in isolated glands or cells, but does stimulate the former in intact animals or isolated mucosal sheets. What is there in the mucosal sheet to account for this difference? This information might bridge the chasm between the results obtained in vivo and in vitro. In isolated *Necturus* mucosa the action of pentagastrin was uninfluenced by a phosphodiesterase stimulant (36). In one study (30) it is claimed that when gastric mucosa from intact animals was analyzed after pentagastrin injection the cyclic AMP levels were increased, but that they were not increased by refeeding following starvation in these same experiments. Two such claims have been made for the rat and one for the dog, but there have been two denials for the rat and one each for guinea pig, rabbit, dog, and humans (13). One has to conclude that it is not known whether histamine or gastrin needs parietal cyclic AMP to stimulate acid secretion. In intact dogs (16), rats, and humans (15) intravenous cyclic AMP or dibutyryl cyclic AMP have been shown to depress both histamine and gastrin-stimulated acid secretion (37). We do not know, therefore, whether gastric acid secretion can be stimulated without an elevation of parietal cell cyclic AMP.

Do augmenters of parietal cell cyclic AMP increase the responsiveness to stimulants? In the case of histamine in isolated preparations this seems to be so with either xanthines or dibutyryl cyclic AMP, which itself stimulates aminopyrine uptake in parietal cells (26), but there is evidence from mucosal sheets in pigs (38) and from isolated gastric glands (39) that this is not consistently so even for histamine. In both of these studies cyclic AMP levels fell with time but acid secretion and aminopyrine uptake reached plateaus. Soll (28) has claimed histamine potentiation of gastrin and carbachol effects on the O_2 consumption of parietal cells, but this is not convincing and has not been confirmed.

Does this work aid in our understanding of the action of secretagogues? What of the final common pathway idea for histamine? Since in isolated parietal cells neither cholinomimetics nor gastrin seems to act at all to increase acid or raise cyclic AMP, we have no evidence for this. Equally, we have no evidence for the specific receptor theory, and negative evidence for the idea that gastrin and cholinomimetics act at all directly on the parietal cell.

The immense amount of work done on this subject seems to have added little but uncertainty in the course of the past 10 years. We seem almost to have reached the stage of frantic stagnation that has characterized some controversies in the past—for instance, the question of the antral inhibitory hormone—before the question was dropped unsolved, remaining as obscure as ever, in fruitless exhaustion. It is my impression that high-fashion situations such as this rarely produce anything definitive. A breakaway is needed, a new methodology. Similar studies on the pancreas have been much more productive because they have a direct measure of acinar activity. I am amazed at the acceptance for the past 10 years of such a dubious and questionably controlled measure as aminopyrine uptake as the sole determinant of acid production. Oxygen consumption is even more questionable.

Since acid production can be measured directly in whole animals and the mucosa is easily accessible, many of the problems mentioned above could be resolved quickly—for instance, do pentagastrin, secretin, glucagon, and so forth raise parietal cell cyclic AMP or affect the involved enzymes? Give the agents, take a biopsy, separate the parietal cells, and analyze them. I would find creditable data of this sort and attempts to resolve the inconsistencies between the cell, isolated glands, mucosal sheets, and the whole animal. As a physiologist and as a teacher I think both are vital; but those working on isolated cells seem uninterested in making a connection—the isolated cell has become an end in itself. Those working on salivary glands study β-adrenergics, but secretory nerves in vivo are cholinergic; secretin stimulates pepsin secretion in vivo but secretin is not studied in vitro because it does not, and so forth. What do we tell students? Surely, for the medical student, what actually enters the gut and the things that stimulate the gut must have priority over cyclic AMP stimulators or calcium mobilizers in vitro when there are discrepancies.

Scientific Fashion and Negative Evidence

A very distressing aspect of this subject is that many publications start off with an air of certainty, and negative results, when they occur, are excused as being due to cellular contamination, impaired circulation, and the like. It is rare to find a manuscript based on isolated cells or glands in which the possibilities are raised that cyclic AMP is not involved in gastric acid secretion and that aminopyrine uptake is an unreliable measure of acid secretion. Fashions do tend to obscure negative evidence.

The observation from these studies which seems to be supported by the most evidence is that xanthine derivatives do decrease phosphodiesterase activity and usually cause acid secretion. From the point of view of the whole-animal gastric physiologist, this is unique. The possibility that these two actions have nothing to do with each other does not seem to have been examined, but we have noted that papaverine, which does the same, did not increase acid secretion from fundic mucosa in dogs (15), and imidazole, which activates phosphodiesterase, did not suppress pentagastrin-stimulated acid secretion from *Necturus* gastric mucosa (36). There are some 20 classes of agents that inhibit phosphodiesterase and at least 4 or 5 that activate it. For very few of these has any consistent action on gastric secretion been described (40). Xanthines have many actions that do not seem to depend on phosphodiesterase inhibition and that are much more sensitive to the agent than is inactivation of the enzyme; an example is their action on heart muscle (41). Support is given to this idea by the finding that cyclic-AMP-dependent protein kinase, the main pathway for cyclic AMP action, is poorly activated in parietal cells by either histamine or isobutylmethylxanthine (42). Indeed, it is maintained that in the parietal cell there is insufficient cyclic AMP generated to activate protein kinase, but there is enough in the mucous cells. Furthermore, it is argued that histamine itself is incapable of increasing cyclic AMP in guinea pig parietal cells without isobutylmethylxanthine, as it does in mucosal cells, but it does increase aminopyrine uptake (34).

Why then is this subject so popular? Perhaps because the pursuit of the small in biology has always implied more intelligence than pursuit of the large. Perhaps investigators are fearful of surgical interference in large animals, or perhaps they do not like to handle animals at all. The current political climate in the United States is not encouraging to those who would use experimental animals in vivo. Maybe, and most importantly, it is easiest to get research funding for this type of work. Why should this be so? Undoubtedly, precisely because the subject is popular. The peer review system of grant awards lends itself to positive-feedback reinforcement of current fashions.

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Lymphoma of the Pancreas

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Abstract

Lymphoma of the pancreas is a rare neoplasm. It should be considered in the differential diagnosis in patients with lesions in the body or tail, especially when associated with chylous ascites, when needle aspiration shows predominantly lymphocytes and not adenocarcinoma, and in patients known to have diffuse lymphoma. Since lymphomas, as well as other malignancies of the body and tail of the pancreas, are at present surgically incurable and laparotomy with biopsy of the pancreas is not without risk, an attempt may be made to establish a diagnosis without surgery. When evidence is strongly suggestive of lymphoma, a therapeutic trial of chemotherapy/radiotherapy is one method of helping to substantiate the diagnosis, since lymphomas are exceptionally responsive to this form of therapy.

The predominant neoplasm affecting the pancreas is adenocarcinoma. The incidence of malignant neoplasms arising from other stem cells is so small that they are rarely considered in the differential diagnosis. Lymphoma arising primarily in the pancreas is one such neoplasm and constitutes approximately 0.16% of pancreatic malignancies (1).

A diagnosis of lymphoma of the pancreas should be considered in several clinical situations:

- when a mass develops in the pancreas in a patient known to have disseminated lymphoma;
- when needle aspiration of a pancreatic mass reveals lymphocytes and no evidence of adenocarcinoma;
- when a pancreatic mass is associated with chylous ascites.

It is important to establish a definitive tissue diagnosis when possible, in order to institute appropriate therapy. With pancreatic lesions this poses a problem, since laparotomy with formal surgical biopsy of the pancreas carries significant morbidity and mortality. The risks and benefits must be carefully evaluated in each patient.

Case Reports

Case 1. A 63-year-old black woman was first seen in November 1983 for evaluation of pain, weight loss, and an upper abdominal mass present for six months. The pain was midepigastric, awakened her at night, was worse after eating, and felt better when sitting up and leaning forward. There was associated constipation and a weight loss of 20 lb but no nausea, vomiting, jaundice, hematechezia, dark urine, or light stools. She had a history of significant alcohol intake over many years.

Physical examination revealed a well-developed, thin woman in no acute distress, with evidence of recent weight loss. A bilobed firm mass was palpable in the midepigastric region extending caudad and to the left of the midline, each segment measuring approximately 5–6 cm in diameter. There was a transmitted aortic pulsation.

An abdominal sonogram done one month before was reported as normal, and a CT scan showed the pancreas to be at the upper limit of normal with a questionable mass in the tail.

A diagnosis of carcinoma of the body and tail of the pancreas was made on clinical grounds.

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Since there are no documented cures with surgical resection of carcinoma of the body or tail of the pancreas, it was planned to confirm the diagnosis by percutaneous skinny-needle aspiration biopsy and if confirmed to treat her with chemotherapy/radiotherapy.

She was admitted to the Beth Israel Medical Center on January 9, 1984. Laboratory data revealed hemoglobin, 10.0 gm/100 ml; hematocrit, 30.7%; white blood cell count, 4,900/cu mm, with 78 polys, 12 lymphocytes, 7 monocytes, 1 eosinophile; alanine aminotransferase, 58 U/L (0–45); aspartate aminotransferase, 24 U/L (0–41); lactic dehydrogenase, 240 U/L (60–200); alkaline phosphatase, 130 U/L (30–115); amylase 292 IU/L (23–85); carcinoembryonic antigen, 2.9 ng/dl.

ERCP was unsuccessful because of partial obstruction of the second portion of the duodenum by an extrinsic mass pressing on the medial wall. CT scan showed the pancreas to be diffusely enlarged, with a mass present at the junction of the body and tail, a moderate amount of ascites, and a normal liver, gall bladder, and bile ducts. Bipedal lymphangiograms, bone scan, and gallium scans were performed but were nonspecific. Several skinny-needle aspiration biopsies of the pancreas, under CT control, were reported as "negative for malignant cells, mostly blood" on both cell block and cytologic smears.

Since a diagnosis of carcinoma could not be cytologically confirmed and there was a history of alcoholism plus an elevated serum amylase value, pancreatitis could not be completely excluded. Inasmuch as she was only mildly symptomatic at this time, she was discharged without further therapy.

She returned for follow-up one month later, and at this time her abdomen was distended by ascites. The ascites became progressively worse despite salt restriction and diuretics; she developed exertional dyspnea, anorexia, and abdominal discomfort.

She was readmitted to the hospital and abdominal paracentesis was performed. Two liters of milky ascitic fluid were removed. Analysis showed it to have an amylase content of 23 IU/L, triglycerides 720 mg/dl, CEA level of 0.03 ng/ml, and proteins 2.8 g/dl. Cytologic examination of a cell block was reported as "Numerous lymphocytes and reactive mesothelial cells. The diagnosis of a lymphoproliferative disorder should be considered."

Since her lesion was not considered surgically curable and there is a high association of chylous ascites with lymphoma, it was decided to institute a therapeutic trial. Vincristine, prednisone, and Cytoxan therapy was begun.

After the initial cycle, the prednisone was stopped and she was discharged to be followed up as an outpatient. Within four weeks the ascites was considerably decreased; by the eighth week it was no longer clinically detectable. The pancreatic mass in the upper abdomen previously obscured by the ascites was again palpable. Six weeks later, discrete skin nodules, varying in size from 0.5 to 1.0 cm, began to appear on both feet, hands, and forearms. One of these lesions was biopsied and was reported to show "superficial and deep perivascular lymphohistiocytic infiltrate."

With continuation of therapy her skin lesions gradually improved, and disappeared completely within three months. At present she has regained weight not related to fluid accumulation, her ascites is gone, the pancreatic mass is no longer palpable, and her skin lesions have resolved. She has been continued on a regimen of biweekly vincristine and oral Cytoxan, has no pain and is doing well three and a half years after she first presented herself for a second opinion on surgical intervention and four years after the onset of her symptoms.

Case 2. A 73-year-old white woman was admitted to the hospital in October 1981 complaining of crampy abdominal pain of three weeks' duration and the passage of stool per vagina. For the past 2 years she had been ill with crippling rheumatoid arthritis, severe vasculitis, and gangrene of her toes. She had been treated with salicylates, gold, and penicillamine. Her history included a myocardial infarct and a hysterectomy.

Physical examination revealed an anxious woman with arthritic changes of both hands and dry gangrenous ulcers of the tips of her toes. The abdomen was flat and nontender, and no organs or masses were palpable. Her vagina was atrophic and contained stool and a 0.5-cm area of granulation tissue was noted at its apex. No pelvic or intrarectal masses were palpable.

Laboratory data showed hemoglobin, 8.5 gm/100 ml; hematocrit, 26.3%; white blood cell count, 11,400 cu mm, with 50 polys, 19 basophiles, 25 lymphocytes, and 6 monocytes. All other values were normal except for a low albumen of 2.6 g/dl. Urinalysis revealed many white blood cells and bacteria.

Chest X-ray revealed interstitial infiltrates in both lower lung fields, heart enlargement in the transverse diameter, and osteoarthritic changes of the thoracic spine. The EKG was consistent with an old anterior myocardial infarction. Barium enema showed recto-sigmoid diverticulosis and a sigmoid-vaginal fistula. Colonoscopy confirmed the diverticulosis, and showed an area of erythema at 30 cm, presumably the site of the fistula.

After appropriate preparation she underwent laparotomy. Exploration revealed the sigmoid colon adherent to the dome of the vaginal cuff at the site of the fistula, a 5 × 3 × 2 cm right ovarian cyst, and an unexpected 10 × 8 × 3 cm rubbery mass in the pancreatic tail adjacent to the splenic hilus. An en bloc distal pancreatectomy and splenectomy was performed, the ovarian cyst and the sigmoid colon were resected, and the sigmoid-vaginal fistula disconnected. Pathologic examination showed the pancreatic tumor to be a histiocytic lymphoma involving the tail of the pancreas, focally invading the spleen and present in one of five regional nodes. The ovary contained a simple cyst and the sigmoid colon showed diverticular disease with fistula formation.

Postoperatively she had a pulmonary embolus to her right lung which was treated with anticoagulants. She refused further studies for staging, chemotherapy, or radiotherapy, citing the poor quality of her life because of her crippling arthritis, and she was discharged. Four months later she succumbed to her rheumatoid arthritis and vasculitis. Autopsy permission was denied.

Discussion

Lymphoma of the pancreas is a rare neoplasm and constitutes only 0.16% of pancreatic malignancies (1). Only 23 cases of so-called primary lymphoma of the pancreas have been reported in the world literature dating back to 1882 (2).

The sex distribution is about the same as pancreatic carcinomas, with a male preponderance of about 5:3. The age range is somewhat younger, with a median of about 64 years and a range from newborns to persons in their 80s.

The location is the same as carcinoma—anywhere in the pancreas from head to tail; symptomatology depends on anatomic location. Preoperatively, most are diagnosed as adenocarcinomas. although some have been confused with pancreatic pseudocysts and cystadenocarcinomas. They are difficult to differentiate from anaplastic carcinoma. Ackerman (3), reporting on 6 cases of lymphoma or pseudolymphoma of the pancreas, found only 1/6 was a true lymphoma; 3/6 had the pancreatic lesion as part of a multifocal lymphoma, and 2/6, originally recorded as primary lymphoma, were ultimately reclassified as anaplastic carcinoma.

Extranodal presentation of non-Hodgkins lymphoma as the first sign of diffuse disease occurs in 21% to 37% of all patients (4). So-called isolated “primary” extranodal lymphoma occurs in only 10% of cases and if followed long enough (15 years), most of these will ultimately prove to have multifocal disease, as happens with “primary” lymphoma of the breast (5). Our Case 1 similarly proved to have multifocal disease.

Since these lesions are so rare, the diagnosis must first be suggested by either tissue examination, cell cytology, or high clinical suspicion, or a combination of these. Biopsy of the pancreas is not without risk, as surgeons well know. The complication rate of laparotomy with pancreatic biopsy ranges from 0%–10%, depending on whether it is done by skinny-needle aspiration transduodenally, with a core-needle biopsy, or by scalpel (6, 7), and is lowest with skinny-needle aspiration. However, aspiration and core biopsy frequently yield inadequate tissue to allow the pathologist to differentiate anaplastic carcinoma from lymphoma. Aside from the morbidity, there is a real mortality related to biopsy of up to 1.7%.

When resection for a neoplasm in the head of the pancreas is contemplated, biopsy is done at the time of laparotomy to avoid a major resection for benign disease. If the biopsy shows lymphoma, the diagnosis is established, and appropriate nonresectional therapy can be instituted. When a neoplasm is present in the body or tail of the pancreas, laparotomy is often not done since cure is remote unless a cystadenocarcinoma or an endocrine tumor is suspected. Occasionally exploration during laparotomy for other cause will serendipitously reveal a mass in the pancreas, as in Case 2, and resection or biopsy is performed as the situation permits.

A high index of suspicion is still paramount to arrive at a correct diagnosis. Unusual leads such as the chylous ascites in Case 1 help. In this case the literature revelation that lymphoma is the most common cause of chylous ascites in adults (8, 9), coupled with the cell-block finding suggesting a diagnosis of lymphoproliferative disease, gave us support and encouragement to initiate a therapeutic trial.

Today, incurable carcinomas of the body and tail of the pancreas identified by ERCP with cell cytology or skinny-needle aspiration under CT or sonar control are frequently treated nonsurgically.

Unfortunately, as mentioned above, cell cytology is usually inadequate to diagnose lymphoma unless the lesion is associated with multifocal disease or suggested by immunofluorescent staining. Here, when lymphoma is suspected but unproven, the use of a therapeutic trial may be warranted. The clinical response in Case 1 strongly suggested that this was lymphoma in her pancreas, but confirmation of her diffuse disease had to await tissue biopsy of the skin lesions, which appeared later.

The current prognosis for and survival of patients with lymphoma of the pancreas is difficult to ascertain, since most of the cases reported antedate the present era of effective chemotherapy and radiotherapy. The mean survival time without therapy is about four months. Since the advent of chemotherapy and radiotherapy, several patients have been reported as living more than 12 months, and an occasional five-year survivor has been reported.

The patient described here as Case 1 has now survived four years since the onset of her illness and appears to be doing well at this time. Certainly the ability to establish the diagnosis without the trauma and possible morbidity of laparotomy and pancreatic biopsy has added to her well-being and quality of life. It is our belief that there is still a place for "therapeutic trials" in carefully selected cases.

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Survival for 25 Years following Partial Pancreatectomy for Carcinoma of The Body of the Pancreas

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Abstract

We report the case of a 48-year-old man with adenocarcinoma of the body of the pancreas, who has survived more than 25 years following a partial pancreatectomy without evidence of recurrence. The diagnosis was initially suspected and confirmed by demonstration of pancreatic insufficiency and cytologic examinations that were positive for malignant cells. The cytologic findings were most important in leading to excision of the tumor. To our knowledge no such long-term survivors with carcinoma of the body of the pancreas have been reported.

Case Report. A 48-year-old man, a truck driver, noted an 18 lb weight loss over a five-month period associated with vague digestive disturbances, bloating, and passage of frequent foul-smelling stools that flushed with difficulty. Examination findings were normal except for slight tenderness to deep pressure in the left upper quadrant and the midepigastric region of the abdomen. Laboratory data were within normal limits. A secretin pancreatic function test yielded pancreatic fluid which showed malignant cells on cytologic examination (careful scanning of 50 smears), as well as reduced volume, enzymes, and bicarbonate. The test was repeated and showed the same abnormal findings.

The patient was admitted to The Miriam Hospital on August 1, 1960 and was operated on two days later. Exploration revealed a firm umbilicated 2.5-cm mass in the body of the pancreas, about 3 cm to the left of the mesenteric vessels. The head of the pancreas appeared normal. No other gross pancreatic abnormality was noted. Frozen sections of enlarged neighboring lymph nodes were negative for metastatic disease. Exploration of the remainder of the abdomen was negative. The distal pancreas was resected along with the spleen. The line of resection was just to the left of the mesenteric vessels, leaving a margin of 1.5 cm of normal pancreas between the tumor and line of resection. The excised pancreatic tissue showed a poorly defined, firm, nodular area of about 1.3 × 1.0 cm adjacent to the pancreatic duct. Microscopically, this area showed moderately well-differentiated infiltrating duct-type adenocarcinoma formed by moderately enlarged atypical epithelial cells with occasional mitoses (Fig.). Remaining portions of the pancreas showed extensive acinar atrophy with replacement fibrosis.

With the onset of this illness, the patient was found to be diabetic. In the postoperative period, he received insulin and diabetic dietary management. Over the next year or so, he gained weight and noticed a decrease and later clearing of the steatorrhea. For over 25 years, except for his diabetes, he has remained active and well, without evidence of recurrent tumor. A CT scan of the abdomen on September 11, 1985 showed the head of the pancreas to be normal in size with the absence of the body and tail of the pancreas and of the spleen. No metastatic disease was seen.

Discussion. Duodenal aspiration cytology for the diagnosis of carcinoma of the pancreas has been performed since 1949, but it has been largely replaced by newer methods (1). The diagnostic accuracy of cytologic study in patients with cancer

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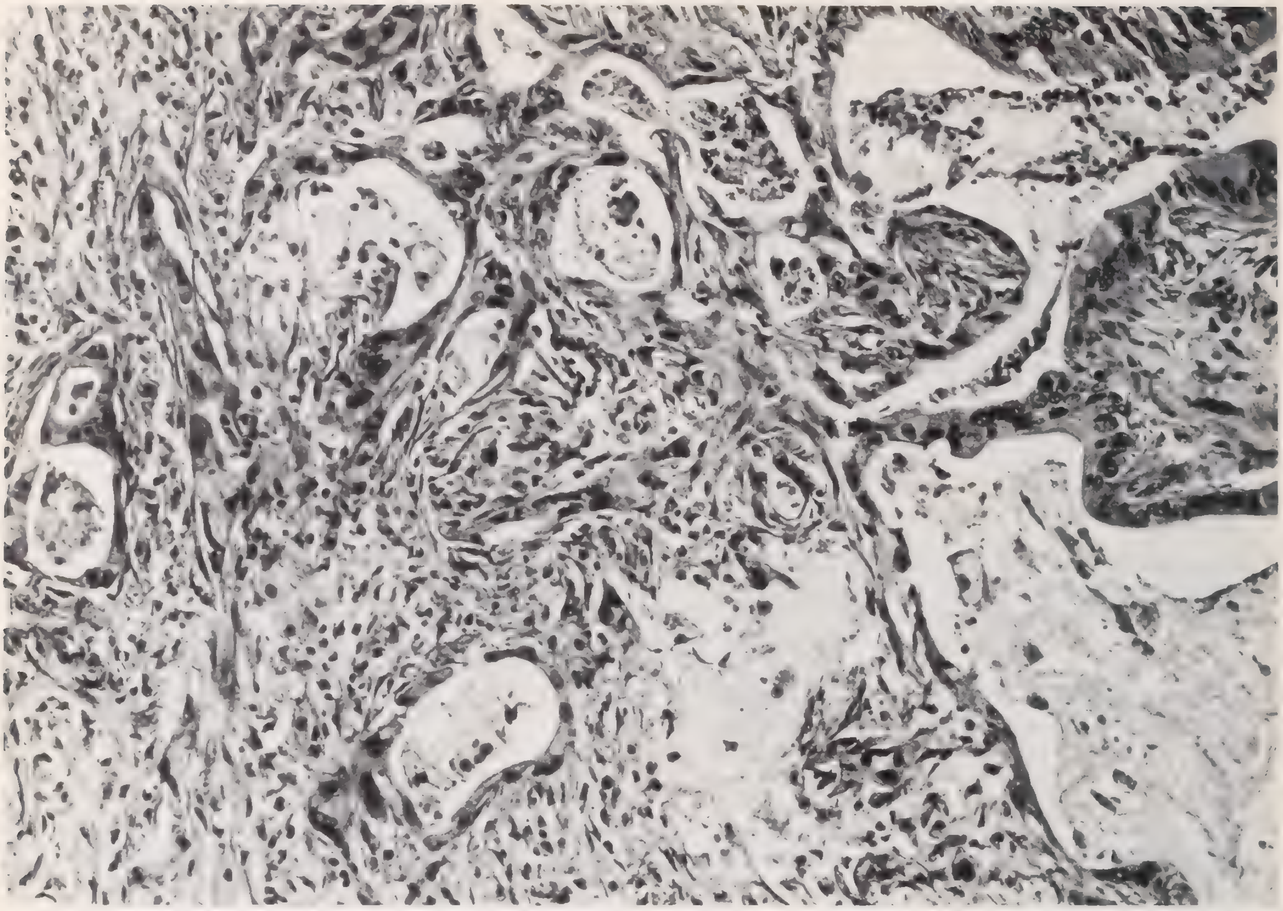

Fig. Section through pancreatic tumor showing infiltrating adenocarcinoma. (Original magnification, ×190.)

of the pancreas is reported as 89%, with 7% false-positive results (2). Gudjonsson et al., in a critical review of 61 reported clinical studies representing about 15,000 patients with pancreatic carcinoma, calculated that the absolute five-year survival rate was 0.4% (3). There has been one reported case of 15-year survival of a patient with an adenocarcinoma of the distal pancreas. It was discovered incidentally during an exploratory laparotomy and removed by wedge resection (4). After a 25-year follow-up of our case, we can report the successful excision of a carcinoma of the body of the pancreas without evidence of recurrence. A high index of clinical suspicion and a properly performed cytologic examination of the pancreatic secretion in this instance made possible the early diagnosis essential for curative surgical excision.

At surgery the lesion was small, located within the pancreatic substance, and without any change in the configuration of the pancreas. It is, therefore, unlikely that had CT scanning and ultrasonography been available in 1960, they would have been helpful in diagnosing this lesion. A recent survey of resectability of carcinoma of the pancreas with the use of the newer diagnostic aids (angiography, CT scanning, ultrasonography, and retrograde cholangiopancreatography) has indicated that their introduction into clinical practice has not permitted an earlier diagnosis of the disease (5).

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Crohn's Disease of the Duodenum Associated with Pancreatitis: A Case Report and Review of the Literature

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Abstract

A 37-year-old white woman with Crohn's ileocolitis diagnosed nine years prior to admission was admitted to The Mount Sinai Hospital after a two-year history of increasing postprandial epigastric burning pain, which became associated with vomiting and left-upper-quadrant pain. Serum amylase one week prior to admission was 1300 IU/liter (40–128 normal). Upper gastrointestinal series showed stricture of the second and fourth parts of the duodenum, and endoscopic retrograde cholangiopancreatogram (ERCP) showed periampullary inflammation and a dilated pancreatic duct. Owing to persistent duodenal obstruction, the patient underwent a Roux-en-Y gastrojejunostomy with truncal vagotomy and demonstrated an excellent clinical response on short-term follow-up.

Crohn's disease of the duodenum is more common than previously thought, but associated complications such as pancreatitis and common bile duct obstruction have been described only rarely. As recognition of Crohn's duodenitis increases, characterization of its potential complications becomes more important. This paper reports the fifth case of Crohn's duodenitis associated with pancreatitis, and discusses pathogenesis and treatment.

Case Report

Nine years prior to admission to The Mount Sinai Hospital, a 37-year-old white woman developed increasingly severe diarrhea and was hospitalized for one month. Upper gastrointestinal series was consistent with Crohn's ileocolitis, and a two-month course of steroids followed by a 2.5-year course of azulfidine resulted in a seven-year remission of symptoms.

Two years prior to admission, the patient developed sporadic postprandial epigastric burning pain, which was treated successfully with sucralfate when symptomatic on two occasions. Three months prior to admission, the patient's pain increased, with no relief from cimetidine. Also at this time the patient began vomiting partially digested food with gradually increasing frequency.

Two months prior to admission, the patient experienced sharp left-upper-quadrant pain, which radiated to the left shoulder and neck, and she was vomiting as frequently as 2–3 times per day. The vomitus now consisted of bright-green thin fluid. A liquid diet was instituted, with some relief of symptoms. Serum amylase was 411. Sonogram at this time revealed an enlarged pancreatic head and body with a normal tail and no evidence of pseudocyst. Repeat amylase one week prior to admission was 1,300.

On admission the patient reported no diarrhea, constipation, melena, hematochezia, or hematemesis and had lost 30 lb over the prior year. No history of hyperparathyroidism, alcohol consumption, 6-mercaptopurine or azathioprine ad-

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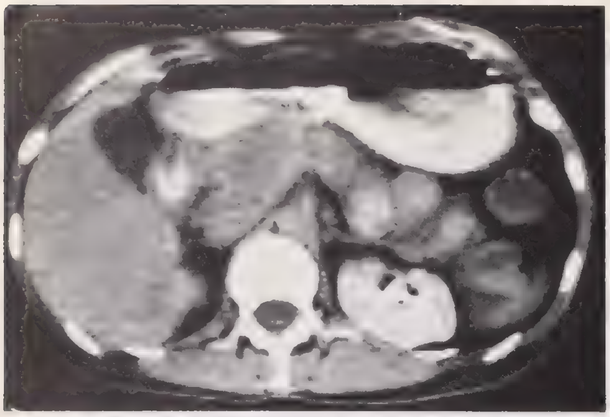

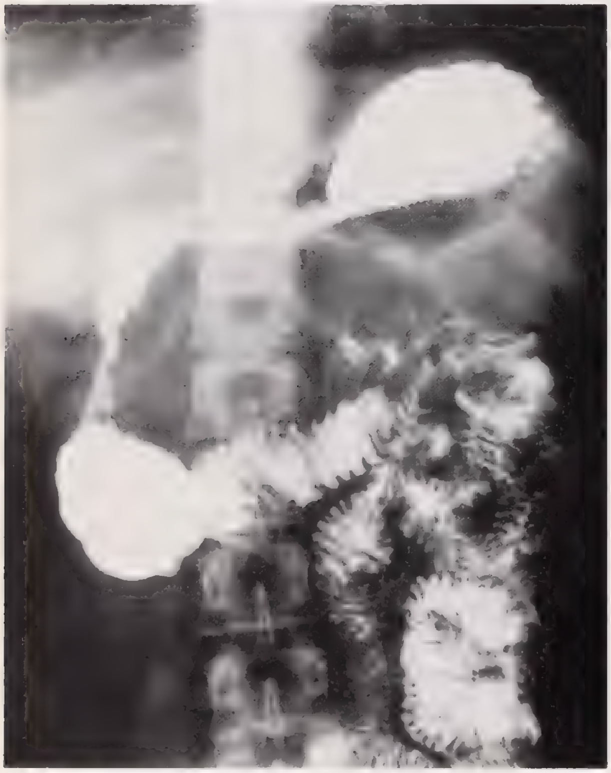

Fig. 1. Top CT scan showing prominent liver, thickened duodenum, and diffusely enlarged pancreas. **Fig. 2. Bottom** Upper GI series showing abnormal duodenal sweep.

ministration, or other risk factors for pancreatitis was noted.

Physical examination revealed a thin, anxious, 37-year-old white woman in no acute distress. She was afebrile with normal vital signs. The abdomen appeared somewhat distended, and a marked succussion splash was appreciated. Bowel sounds were normoactive. There was diffuse mild tenderness on palpation in the epigastrium and right lower quadrant. The liver was palpable 3 cm below the costal margin and measured 6 cm in the midclavicular line. No masses or other organs were palpable. Rectal examination findings were normal and the stool was guaiac negative. Other examination findings were essentially normal.

Laboratory tests showed a microcytic hypochromic anemia—hemoglobin of 9.5 and hematocrit of 29.6. Serum amylase was 255, protein 5.3, albumin 2.8. Alkaline phosphatase, SGOT, SGPT, and bilirubin were all normal.

The patient was begun on a regimen of intravenous hydration only. Further studies included repeat sonogram, which demonstrated the pancreas to be slightly larger than at the previous study, still with no evidence of pseudocyst. Computerized tomography showed a prominent liver, a diffusely enlarged pancreas, and a thickened duodenum (Fig. 1). Upper gastrointestinal series revealed the entire duodenal sweep to be abnormal, with strictures in the second and fourth parts and dilatation of the distal second part (Fig. 2). The stomach was markedly dilated with increased secretions. The small-bowel follow-through was consistent with moderate ileocolitis, and diffuse small ulcers were apparent, most markedly in the transverse colon. Endoscopy showed extensive duodenal Crohn's disease; polypoid inflammation surrounded the ampulla. ERCP demonstrated a dilated pancreatic duct, which tapered to a narrowed segment 3 cm distal to the ampulla; a large accessory duct was present (Fig. 3). Colonoscopy was unremarkable, despite changes noted on the barium enema examination at the time of original diagnosis.

Owing to persistent duodenal obstruction, it was felt that surgical intervention was necessary. Preoperatively, a nasogastric tube, inserted to decompress the stomach, drained 1,350 cc of green fluid per day over 48 hr.

In the operating room, a midline incision was made. The stomach appeared normal, with nasogastric tube palpable in the fundus. The duodenum was examined, and the first and second portions were inflamed with a stricture in the second portion and distention distal to the stricture. The duodenum was not formally Kocherized, and the third and fourth portions were not well visualized. From the ligament of Treitz there was a 15-cm length of jejunal Crohn's disease with strictures at 5 cm and 10 cm. The walls were thickened with characteristic creeping mesenteric fat and diffuse lymphadenopathy in the mesentery. The remainder of the small bowel was normal to the ileocolic junction, where there was a 3-cm segment of mild disease. The colon was normal in its ascending and descending portions, but the transverse colon showed minimal serosal inflammation. The pancreatic head was prominent and indurated, but the body and tail appeared normal. The distal esophagus was normal, and truncal vagotomy was performed. The jejunum was divided 5 cm distal to the segment of Crohn's disease, and retrocolic gastrojejunostomy was performed. To avoid an unacceptably long afferent loop, this was done in Roux-en-Y fashion, with the Roux loop anastomosed 40 cm distal to the gastrojejunostomy. A tube gastrostomy was inserted as well.

The patient had a benign postoperative course, and seven weeks after the operation, she was asymptomatic, had gained 12 lb, and had a normal serum amylase.

Discussion

Crohn's disease of the duodenum is more common than previously thought. In the National Cooperative Crohn's Disease Study, 118 of 535 patients (22%) showed duodenal abnormalities on upper gastrointestinal series, and of these, 41 patients (8% of total) demonstrated a pattern typical of Crohn's disease—narrowing of the duodenal bulb and sweep, thick irregular folds, and shallow ulceration (1). It is not known whether any of these patients had particularly prominent periampullary inflammation or evidence of pancreatitis. A radiologic pattern described by Marshak et al (2) consists of areas of duodenal stenosis with intervening dilated segments, and this is consistent with our case.

Patients with duodenal Crohn's disease who are symptomatic usually have symptoms similar to those of atypical peptic ulcer disease (3). However, in many asymptomatic patients, duodenal involvement is noted incidentally in studies evaluating more common sites of Crohn's disease.

Crohn's disease of the duodenum with acute pancreatitis is quite rare, only four cases having been previously reported (4, 5). Pancreatitis without duodenal involvement in Crohn's disease has been reported, but this is considered to be a drug hypersensitivity reaction secondary to 6-mercaptopurine, azathioprine (6), or possibly steroid administration. Our patient, however, never received 6-mercaptopurine or azathioprine, and her only steroid therapy was nine years prior to the admission described here.

Pathogenesis. The pathogenesis of pancreatitis with Crohn's duodenitis is not clearly understood, but several mechanisms have been described. Altman et al (5) discuss reflux of duodenal contents, either through a stretched, incompetent ampulla or through an inflamed, damaged ampulla with duodenal–pancreatic duct fistula. These possibilities are supported by Legge et al (4), whose three patients exhibited reflux of barium on upper gastrointestinal series into the pancreatic as well as the common bile ducts. In our patient, an inflamed ampulla was apparent on endoscopy, but there was no barium reflux on upper gastrointestinal series. However, transient reflux of duodenal contents may cause an inflammatory reaction in the pancreatic duct with obstruction secondary to stricture of the duct. Finally, the periampullary inflammation in itself can cause pancreatic duct obstruction. This is analogous to the findings in the only reported case of duodenal Crohn's disease causing common bile duct obstruction, in which the ampulla could not be identified on endoscopy owing to periampullary inflammation, and percutaneous transhepatic cholangiogram showed partial obstruction of the intramural duodenal segment of the common bile duct (7).

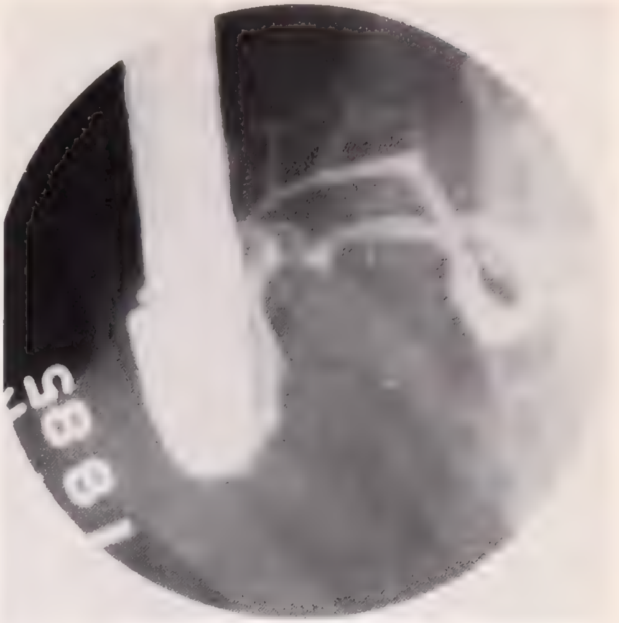

Fig. 3. ERCP demonstrating dilated pancreatic duct tapering to narrowed segment 3 cm distal to ampulla, and large accessory duct.

In addition, it is well known that Crohn's disease has been observed throughout the alimentary tract, but as Altman et al (5) noted, it is not known whether the pancreas can be a site of primary Crohn's disease. However unlikely primary pancreatic Crohn's disease may seem, it is a difficult entity to rule out owing to the inherent hazards of pancreatic biopsy.

Therapy. Medical therapy for Crohn's duodenitis can include enteric rest, steroids, and azulfidine, as well as antacids and cimetidine. However, the efficacy of medical treatment in disease advanced enough to cause acute pancreatitis is questionable—of the previous four cases reported, only one was successfully treated with a medical regimen. If primary pancreatic Crohn's disease exists, its possible response to steroids is interesting to consider.

In the three cases of Legge et al (4), surgical intervention was necessary, consisting of gastroenterostomy. This was successful in two of three patients. The procedure performed in our case was a Roux-en-Y gastrojejunostomy to bypass the diseased segments of duodenum and jejunum and truncal vagotomy to decrease gastric acid secretion. A tube gastrostomy was performed to allow early removal of the nasogastric tube. The importance of vagotomy as part of the surgical treatment of Crohn's duodenitis was demonstrated by Ross et al (8). Of four patients who originally underwent bypass with vagotomy, all remained free of ulcerative complications. However, of six patients who had bypass without vagotomy, three subsequently required vagotomy. If surgical intervention is necessary, we agree that gastroenterostomy with vagotomy is the procedure of choice.

Conclusion

Widespread recognition of Crohn's duodenitis as a not uncommon entity has been a relatively recent development, and the elucidation of various complications of this condition is sure to follow. Despite only four previously reported cases of pancreatitis with Crohn's duodenitis, we believe that such complications may be more common. In a patient with a long history of Crohn's disease, the pain characteristic of pancreatitis (or other complications), unless very acute, may not be distinguished from the chronic pain some Crohn's patients are accustomed to or taken seriously enough by clinicians. The duodenum should be carefully considered in all studies patients undergo for evaluation of Crohn's disease, and in symptomatic patients with duodenal disease, complications such as pancreatitis or common bile duct obstruction should be ruled out. Perhaps early recognition of duodenal disease will allow medical therapy to control the process before surgical intervention becomes necessary.

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Renal Cell Carcinoma in a Polycystic Kidney

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Abstract

A sixty-five-year-old woman with polycystic kidneys on a long-term regimen of dialysis had right nephrectomy for what was preoperatively thought to be a perinephric abscess, but at surgery turned out to be a tumor. Microscopic examination revealed sarcomatoid renal cell carcinoma and classical features of adult polycystic kidneys with focal proliferative changes as seen in long-term hemodialysis. The clinical recognition of a carcinoma developing in polycystic kidneys is often difficult because of the presence of preexisting large renal masses and occasional hematuria in these patients. Renal cell carcinoma should be thought of when confronted with weight loss, abdominal or back pain, severe hematuria, or a new renal mass occurring in a patient with polycystic kidneys. The incidence of carcinoma in polycystic kidney may increase as the average life span of these patients has become longer with hemodialysis.

Renal cell carcinoma developing in a patient with polycystic kidneys is rare, and its clinical diagnosis can be associated with considerable difficulties. The patient described herein was thought to have a perinephric abscess preoperatively. The clinical problems of the diagnosis and management of our patient, a relation of carcinoma to the polycystic kidneys, and the relevance of the microscopic dialysis-related renal changes are discussed.

Case Report. A 65-year-old woman was hospitalized because of a fever and low back pain of two weeks' duration. Congenital adult polycystic kidney disease was diagnosed six years previously, and the patient had been on hemodialysis since then. She reported no recent gross hematuria or changes in appearance or pattern of the urine. On admission, the temperature was 39°C and blood pressure 160/90 mmHg. Both kidneys were easily palpable, but the liver and spleen were not felt. Hematocrit was 23.5%, hemoglobin 7.9 gm/dl, white blood cell count 6,500/cu mm with a shift to the left. BUN was 92 mg/dl and creatinine 8.8 mg/dl. Urine and blood cultures yielded no growth. Abdominal CT scan revealed cystic liver and polycystic kidneys, with a large abscess extending to perirenal area and psoas muscle (Fig. 1). A thick bloody fluid was obtained on percutaneous drainage, but the cultures and cytologic examination yielded no significant findings.

Despite treatment with clindamycin, gentamycin, and Ancef the bloody discharge persisted, along with fever and pain, thus necessitating a surgical exploration. At operation a large tumor was found, involving the posterior part of the right polycystic kidney and adherent to the psoas muscle. Right radical nephrectomy was performed. Subsequently, radiotherapy was given to the right renal fossa, but the patient developed severe intractable pseudomembranous colitis and she died five weeks after the operation. There was no autopsy.

Pathologic Findings. The kidney had the typical appearance of an adult polycystic kidney; it measured 22 × 8 × 8 cm and weighed 750 gm. The posterior aspect of the kidney disclosed a dark red-gray tumor, 12 × 7 cm in size, which extended to and involved the perirenal fat, and

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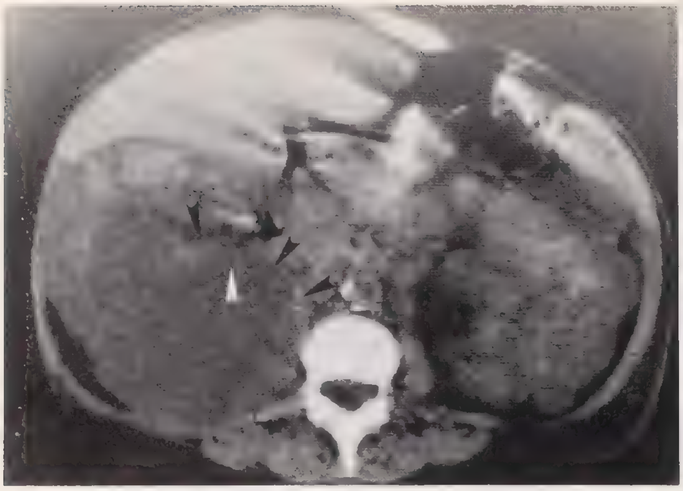


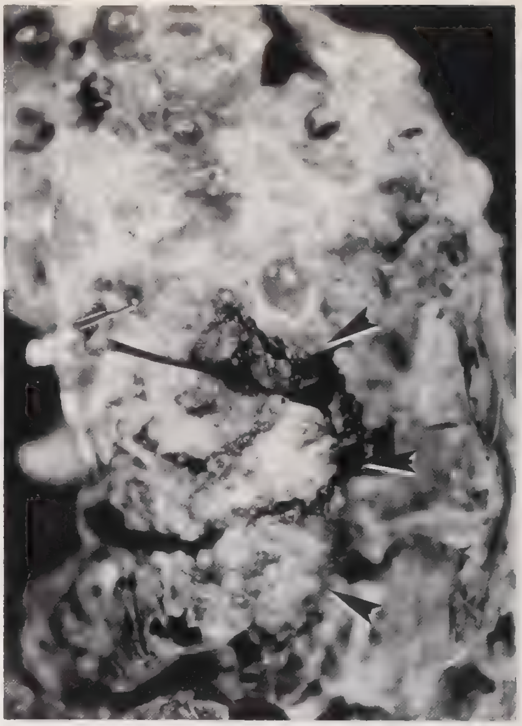


Fig. 1. Left CT scan at upper pole of right kidney shows large low-density collection (black arrow) with probable gas within (white arrow), consistent with renal abscess. Polycystic changes are seen in left kidney. **Fig. 2. Right** Posterior aspect of polycystic kidney showing central area of tumor (arrows). A few cysts are visible above tumor.

showed extensive necrosis (Fig. 2). The renal veins were uninvolved.

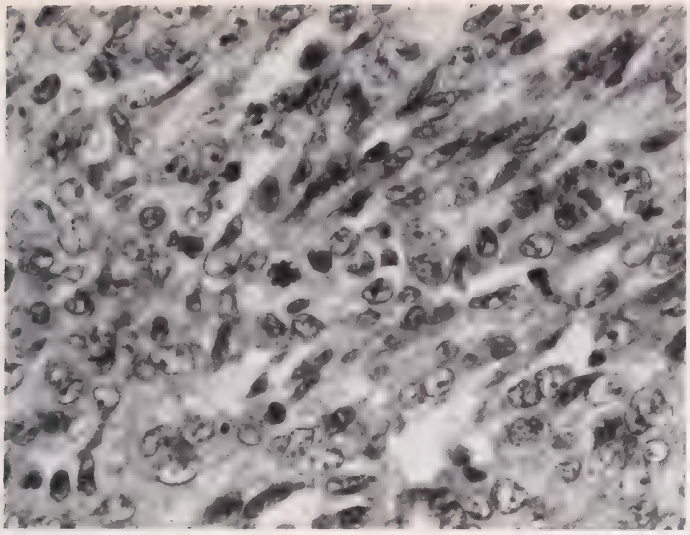
Microscopically, the tumor consisted of pleomorphic spindle cells forming predominantly sarcomatoid pattern (Fig. 3) with only small foci of gland formation. Electronmicroscopic study of the spindle cell areas did reveal primitive intercellular junctions, although no microvilli or desmosomes were seen. Tumor-free renal parenchyma showed numerous cysts with thin septae containing rare sclerotic glomeruli. There were focal areas of benign tubular epithelial proliferation, hyaline arteriolar sclerosis, and papillary epithelial hyperplasia of the cyst lining (Fig. 4), all characteristic of long-term dialysis effect (1, 2).

Discussion. Adult polycystic kidney disease (APKD) has only rarely been associated with renal cell carcinoma; since the original description in 1934 (3) we found a total of 25 reported cases of this association in the literature (4–6). Although the incidence of renal cell carcinoma is increased in the cystic kidneys of Hippel-Lindau's disease (7), our patient did not have any evidence of the latter, such as the cerebellar or retinal symptoms. Nor did we find any indication of the presence of pancreatic or splenic cyst, or berry aneurysm of the cerebral arteries, all of which can be present, in addition to the liver cysts, in patients with APKD (8).

The proliferative epithelial changes seen in the kidneys of patients on chronic dialysis include tubular epithelial hyperplasia (2), adenoma (9), and vascular smooth muscle nodules (10). Similar papillary intracystic epithelial proliferation was seen focally in the renal parenchyma in our patient, who had had dialysis for six years. Long-term dialysis may be a factor promoting development of renal cell carcinoma in patients with APKD, as it is thought to be in patients receiving long-term dialysis in general (11, 12). The carcinoma occurred in our case in a kidney which showed changes of both APKD and long-term dialysis, an association apparently heretofore undescribed.

The sarcomatoid variant of renal cell carcinoma is rather infrequent; it constituted only 1.8% of 2,100 renal cancers in a series from the Mayo Clinic (13). Sarcomatoid renal cell carcinoma in a polycystic kidney is a rarity, since our search of the literature has yielded only one example of this association (4).

It is often difficult to diagnose clinically a carcinoma arising in APKD, probably because these patients have preexisting large renal masses, as well as occasional hematuria. Our patient was thought to have an abscess, and the tumor was diagnosed only at surgery. Although severe bouts of hematuria appear to be a very important sign suggestive of development of a carcinoma (4, 5), this patient instead had low back pain and fever as the main complaints. Compli-



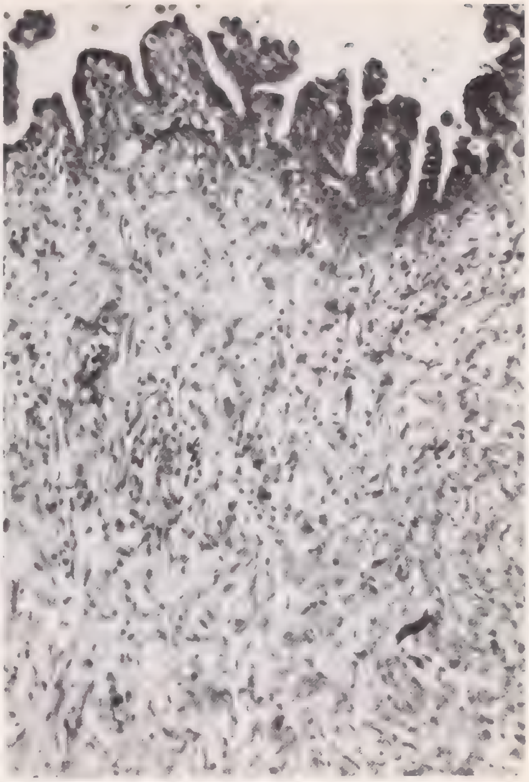


Fig. 3. Left Undifferentiated malignant spindle cells, with mitosis (center). **Fig. 4. Right** Papillary hyperplasia of cyst lining (top).

cations of APKD other than the malignancy and infection include sudden massive bleeding that can result in severe anemia or in ureteral obstruction by a clot, stone formation, and bone and joint disorders; increased incidence of gouty arthritis has also been reported. Of these, renal infection is the most common and potentially life-threatening complication of APKD (14). The tumor in our patient showed extensive central necrosis which led to radiologic misinterpretation as an infected cyst.

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Stercoral Perforation of the Descending Colon Appearing Radiographically As Pneumomediastinum

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Abstract

We present the first reported case of stercoral perforation of the colon presenting radiographically as pneumomediastinum. Radiographic, clinical, and pathologic features of this entity are discussed.

The posterior pararenal space, one of the three subdivisions of the retroperitoneum, is continuous superiorly with the mediastinum via the sheaths of the great vessels (1). Any perforation of a viscus into the retroperitoneum may result in pneumomediastinum in addition to free air in the retroperitoneum. Numerous causes of gastrointestinal pathology resulting in pneumomediastinum have been reported (2–8). We report the case of an elderly woman whose diagnosis of stercoral perforation of the descending colon was initially suggested chiefly by the presence of pneumomediastinum on the admission films. A contrast enema pinpointed the site of perforation, and a computerized tomography scan localized the resultant abscess and the origin of the free air.

Case Report

An 85-year-old white woman was transferred to Beth Israel Medical Center from a nursing home with the chief complaint of increasing abdominal distention over the previous 3 days which was unrelieved by cleansing enemas. The patient, who suffered from organic mental syndrome, chronic congestive heart failure, and hypothyroidism, had been admitted 8 months earlier for a similar complaint, which responded to conservative management and was attributed to fecal impaction. A history of chronic constipation was obtained.

Relevant physical findings included bibasilar rales, distended tender abdomen with normal bowel sounds, and fullness in the left upper quadrant. No masses or organomegaly was palpated. The initial abdominal films (limited by the patient's condition) demonstrated a reflex ileus and a mottled gas collection in the left upper quadrant. The admission chest film (Fig. 1) demonstrated a linear collection of air extending from the midabdomen to the midthorax along the left lateral aspect of the aorta. Endoscopy and gastrograffin swallow (Fig. 2) did not reveal perforation of the esophagus, stomach, or duodenum. An abdominal scan (Fig. 3) demonstrated the abscess collection in the left flank. In addition, air was noted in the left anterior pararenal space and left posterior pararenal space as well as paraaortic air beneath the diaphragm, extending to the mediastinum. A contrast enema (Fig. 4) demonstrated a posteriorly directed perforation in the middescending colon. No diverticula or mass lesions were noted.

The patient underwent laparotomy 6 days after admission. An area of induration and necrosis of the mesenteric aspect of the descending colon was noted. A significant amount of free stool was not evident. The descending colon was resected, and proximal and distal colostomies

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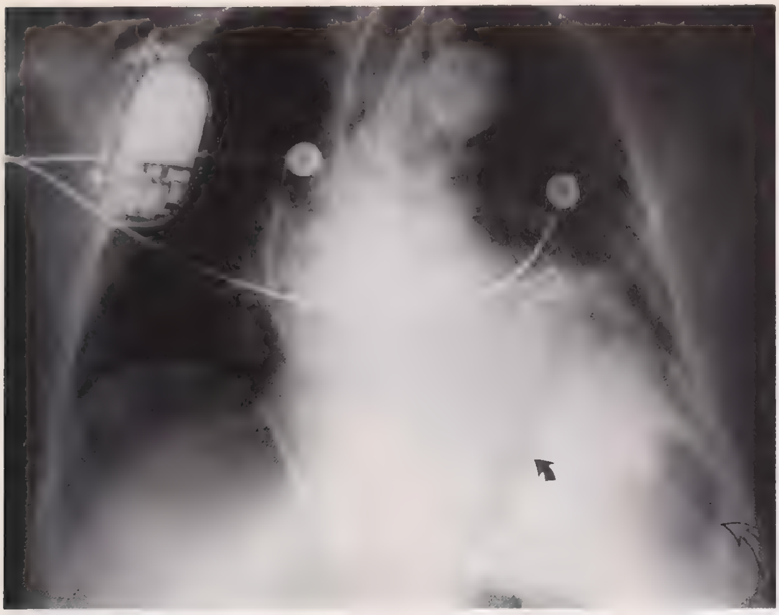


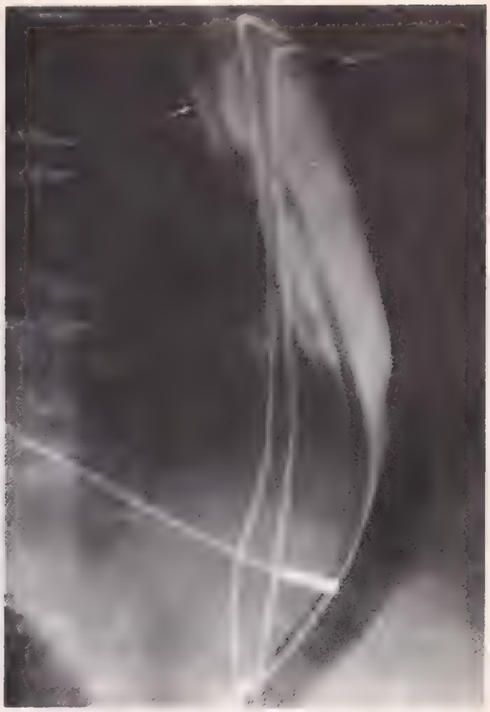
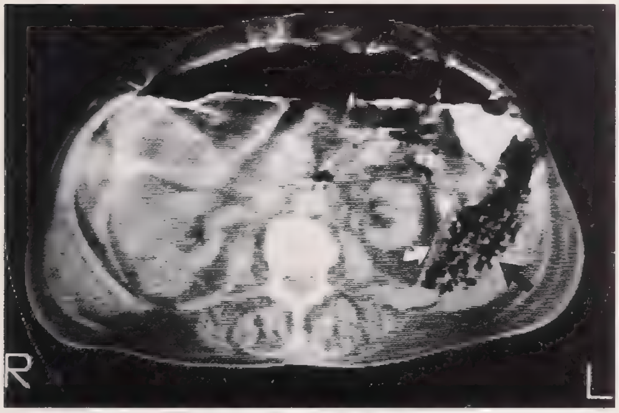


Fig. 1. Left Admission chest film demonstrates curvilinear air collection extending between upper abdomen and mediastinum along left lateral border of aorta (black arrow). Also note mottled air collection in left upper quadrant (open arrow).
Fig. 2. Right Gastrograffin swallow does not reveal extravasation. Air collection again noted and is shown to be anterior to and separate from esophagus.



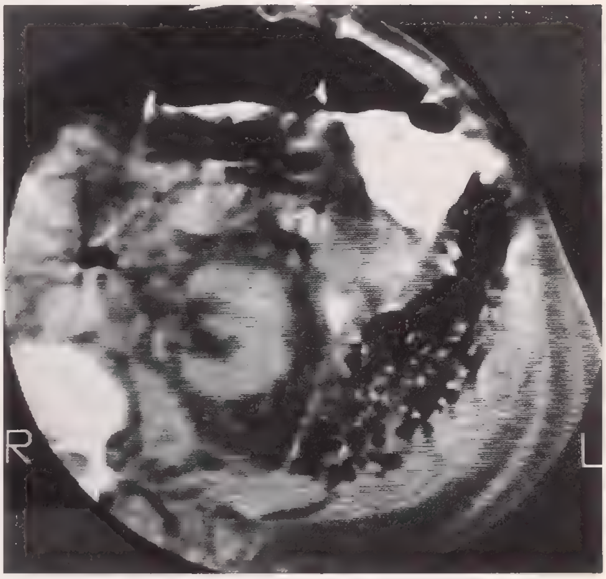


Fig. 3. Left CT scan at level of kidneys reveals abscess collection in left flank, apparently arising from collection in posterior aspect of anterior pararenal space (APRS) behind colon (black arrow). Note preservation of Gerota's fascia (white arrow). Right renal cyst also demonstrated. **Right** Magnified view at same level; detail of relationship of abscess to colon and APRS.

were performed. Pathologic examination of the resected colon revealed a perforation in the posterior wall which measured 2.5 by 1.5 cm. The mucosa peripheral to the perforation was indurated. The surrounding serosa was covered with a green-white fibrinoid material. The vasculature was examined and appeared normal.

Discussion

In our patient, the history of recurrent obstruction due to fecal impaction and the pathologic findings of a large perforation with surrounding necrosis in the absence of other pathology are all suggestive of stercoral ulceration

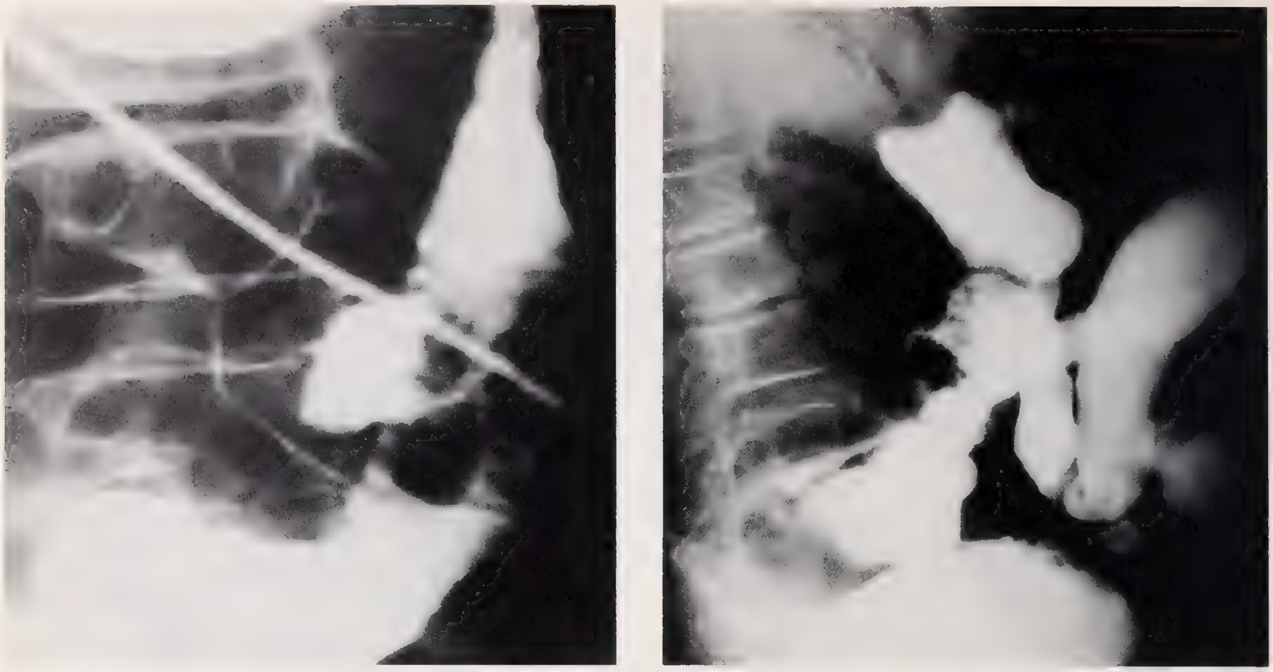


Fig. 4. Left Spot film from contrast enema reveals large posterior perforation in mid-descending colon. **Right** Perforation is demonstrated, with anterior displacement of descending colon by abscess.

as the cause of the perforation. The lack of gross free feces, a usual finding in this entity, can be explained by the cleansing enemas given in the nursing home. This entity is a rare cause of colonic perforation; only 30 cases have been reported since 1894 (9). It involves mechanical ulceration of the mucosa by impacted feces. In extreme cases, necrosis and perforation result. The most common site is the rectosigmoid region, and it usually occurs in debilitated elderly patients with chronic constipation. The prognosis is poor, only 60% surviving after surgery.

This entity should be differentiated from idiopathic perforation of the colon (10), another constipation-related condition resulting from sudden increased intraluminal pressure rather than mechanical erosion. These entities can be differentiated by the pathologic appearance. The idiopathic perforation site is surrounded by normal mucosa, whereas in stercoral perforation, the surrounding mucosa is necrotic. We were unable to find other reports describing pneumomediastinum resulting specifically from this entity.

The exact course of the gas from the perforation site to the mediastinum in this case is somewhat uncertain. The accepted mode of dissection put forth by Meyers (1) is passage from the inferior anterior to the posterior pararenal space and then superiorly along the sheaths of the great vessels to the mediastinum. We cannot exclude such a pathway in this patient. However, one would expect to see air in the left perirenal space were this the case, and this was not seen on the CT scan. This study appears to reveal dissection from the perforation site in the posterior aspect of the anterior pararenal space directly medial to the periaortic sheath and then superiorly to the mediastinum. The patient was symptomatic for 3 days prior to admission, and the scan was performed 4 days after admission. The large left flank abscess was readily apparent. Infection has been postulated as a favorable factor for abnormal anatomic transgression of air (11), and this may explain the course of air in this patient. Alternatively, congenital or acquired defects in the fascial layers may explain this occurrence (2).

Perforation of the anterior aspect of either the ascending or descending colon would result in free intraperitoneal air, as these segments are covered by peritoneum. The posterior aspects of these segments are not covered by peritoneum, so rupture occurs into the posterior portion of the anterior pararenal space. The admission films suggest the diagnosis of retroperitoneal visceral perforation by the presence of pneumomediastinum and a mottled gas collection in the left upper quadrant. It has been noted (1) that retroperitoneal air appears mottled as compared to the homogenous appearance of free intraperitoneal air. Subdiaphragmatic air may be retroperitoneal, but it will not extend superiorly as high as intraperitoneal air.

Immediate identification of pneumomediastinum resulting from retroperitoneal visceral perforation is critical in view of the high mortality. Several imaging modalities may be used. Barium studies may pinpoint the site of perforation. CT scan is capable of identifying the abnormal collection and delineating its extent; in addition, it may suggest the site of origin in the abdomen and the location of any resultant abscess.

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Multiple Spontaneous Perforations of the Small Intestine

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Nontraumatic multiple free perforations of the small bowel are uncommon. In the United States, perforation of the small bowel in adults is generally associated with obstruction, gangrene, or trauma. Generalized peritonitis due to perforation of the small bowel in the absence of one of these conditions is rare. Other documented, but less common, causes of spontaneous small-bowel perforation are foreign bodies, Crohn's disease, jejunal diverticulosis, lymphoma, metastatic cancer and cancer chemotherapy, Meckel's diverticulum, steroid ingestion, and perforations of unknown etiology (1, 2).

This article reviews several of these etiologies. In addition, a case of multiple small-bowel perforations of unexplained etiology is presented and discussed.

Case Report

A 77-year-old black woman was admitted to the medical service complaining of nausea and vomiting of 6 days' duration, as well as progressive weakness during the week prior to admission. She reported no hematemesis or diarrhea. There was no history of peptic ulcer disease, colitis, or alcohol abuse. Significant medical history included 10 years of hypertension, hepatitis A many years prior to admission, mild renal insufficiency, and rheumatoid arthritis. She was taking methyldopa and piroxicam. Prior surgery included an umbilical herniorrhaphy, a hysterectomy many years previously, and bilateral knee replacements 5 years prior to admission.

Physical examination revealed a blood pressure of 80/40, temperature of 97°F, and pulse rate of 104. The abdominal examination revealed a soft, nontender, mildly distended abdomen, with normal bowel sounds and no organomegaly. Rectal examination revealed guaiac-positive stool. The hemoglobin was 15.7 mg/dl and the leukocyte count 9000, with 83 segmented neutrophils, 12 lymphocytes, 3 basophils, and 2 monocytes. BUN was 148 and serum creatinine was 6.0. Urinalysis was unremarkable. A chest x-ray was normal, and abdominal films revealed a nonspecific small-bowel gas pattern.

The patient was admitted for observation and hydration. On the first hospital day she vomited feculent material and complained of epigastric discomfort. Physical examination at this time revealed diffuse abdominal tenderness without guarding or rebound and absent bowel sounds. The surgical consultant advised prompt laparotomy after resuscitation.

Surgery revealed a small-bowel obstruction secondary to an adhesive band. The bowel was moderately dilated proximally. Two free perforations of the ileum on the antimesenteric border, approximately 5 cm and 30 cm proximal to the obstruction, were noted (Fig. 1). A segment of bowel, including both sites of perforation, was resected, and end-to-end anastomosis was performed.

The patient was improving when, on the fourth postoperative day, feculent drainage was noted from the wound. On reexploration a new perforation distal to the anastomotic site was found. The anastomosis was intact. The remainder of the small bowel appeared normal, and there was no evidence of distal obstruction. Another end-to-end anastomosis was constructed after resection of the perforated bowel segment.

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The patient initially did well, but on the third postoperative day she began to exhibit evidence of diffuse coagulopathy. This was treated with appropriate replacement; on the fifth postoperative day she became hypotensive and exhibited signs of peritonitis. She was reexplored and an identical free perforation of the ileum was discovered in the segment between the previous anastomoses. Leakage from the initial anastomosis was also noted. The segment of bowel containing both anastomoses was resected, and the patient was left with a single end-to-end anastomosis.

She remained septic postoperatively and did poorly. Her coagulopathy worsened and she began to bleed massively from diffuse gastritis. She died on the sixth postoperative day. A postmortem examination was not performed.

Pathologic evaluation of the resected specimens revealed "bowel showing acute perforation. The blood vessels displayed no significant change and there was no evidence of vasculitis. Bacterial colonies were present on the serosa. There were also areas of mucosal hemorrhage" (Fig. 2). Stains and culture for fungi were negative.

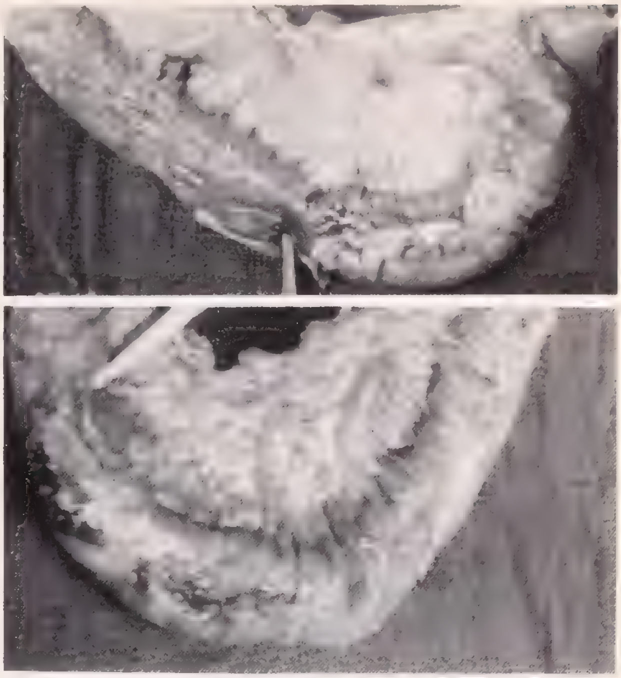

Fig. 1. Segments of bowel, 25 cm apart, showing areas of perforation on antimesenteric border.

Discussion

Worldwide, typhoid fever is the most common cause of small-bowel perforation, but this is rare in developed countries (3). The commonest causes of small-bowel perforation are adhesive bands, hernias, and trauma. Less frequent etiologic factors include foreign-body perforation, tumor growth, Crohn's disease, steroids, and chemotherapy. Additionally, there have always been some cases of undetermined etiology.

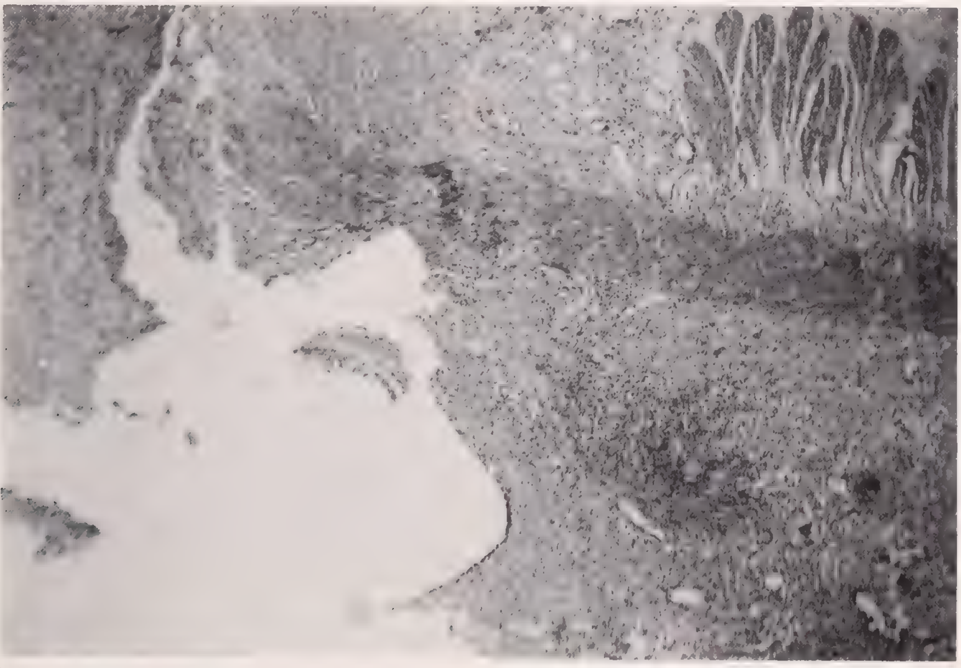

Fig. 2. Photomicrograph of area of perforation with surrounding tissue necrosis and lymphocytic infiltrate (original magnification ×10).

Although foreign-body ingestion is common, consequent injury to the intestinal tract is uncommon, even when the ingested object is sharp; intestinal perforation occurs in under 1% of cases. McPherson et al (4) noted a correlation of foreign-body perforation with advanced age. They attribute this primarily to the widespread use of dentures in the elderly population with absent palatal sensation.

Intestinal perforation secondary to malignancy is increasing in frequency (2). These perforations have been related to the presence of both intrinsic and extrinsic malignancy in the bowel, causing partial or complete obstruction. Additionally, in patients with infiltrating malignancies, such as lymphomas, perforation may occur owing to the rapid lysis of the tumor during chemotherapy (5).

A study of 387 patients with Crohn's ileitis admitted to the Mount Sinai Hospital over a 20-year period revealed 4 patients with free perforation (6). In all these cases the perforation originated in an area of active jejunal or ileal inflammation with distal obstruction.

Huttunen et al (7), in reviewing 24 patients with small-bowel perforation, found a perforated Meckel's diverticulum in 3 patients and an isolated ileal diverticulum in a fourth patient. Ulceration is the most common cause of Meckel's perforation, but it may also occur secondary to foreign-body ingestion, intussusception, infection, or strangulation.

Malignant atrophic papulosis of Degos is a cutaneovisceral syndrome characterized by pathognomonic umbilicated white papules with elevated telangiectatic borders, followed by the development of intestinal ulcers that perforate. The arterioles in the lesions occlude by endothelial proliferation. In the review of Huttunen et al (7), 2 of 24 patients studied over a 15-year period had malignant atrophic papulosis with perforations of the small bowel. Both patients had multiple perforations, as well as several deep ulcerations of the bowel.

Rushovich (8) describes a patient in whom widespread atheroemboli to the bowel resulted in focal jejunal necrosis and subsequent perforation of the jejunum. It is not uncommon for the gastrointestinal tract to be involved in atheroembolism. The bowel may be involved at any site, and the lesions may range from superficial mucosal ulcerations to mucosal infarcts and subsequent perforations.

Periarteritis nodosa, among other connective tissue disorders, has been implicated as an uncommon cause of small-bowel perforation (9). Also, steroid administration has been implicated in small-bowel perforation, possibly because of steroid interference in the healing process in a regenerating organ.

A review by Adler et al (10) reports 2 patients with rheumatoid arthritis in whom necrosis of the small bowel developed secondary to acute necrotizing mesenteric arteritis. Although involvement of small vessels has been found in a variety of tissues, it is infrequent in the arterioles of the small-bowel mesentery. Intestinal necrosis secondary to the arteritis of rheumatoid arthritis is a possible etiology in the case we have presented, although the pathologic findings did not confirm this. An arteritis could have been missed owing to the limited segmental distribution of the vascular lesions (11). This would, however, explain the occurrence and recurrence of multiple spontaneous perforations of the bowel with no obvious gross or histologic pathology.

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Student Corner

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Enteric Tuberculosis: Literature Review

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Since antiquity tuberculous enteritis has been recognized as a serious, and often fatal, complication of pulmonary tuberculosis. Hippocrates warned that "phthisical persons die if diarrhea sets in" (1). In the 19th century surgeons reported isolated granulomatous lesions of the intestines, presumed to be tuberculous, third in incidence only to malignant and acute inflammatory diseases of the abdomen (2). Improvement in sanitary conditions, pasteurization of milk, and introduction of antituberculous chemotherapy have made this once common entity a clinical rarity.

Abdominal tuberculosis lacks classical clinical features; it may mimic a vast array of intestinal disorders. Clinicopathologic manifestations of abdominal tuberculosis may be divided into three categories: gastrointestinal tuberculosis, ulcerative or hypertrophic; tuberculous peritonitis and ascites; and mesenteric lymphadenitis (2, 3).

This review of literature on abdominal tuberculosis centers primarily on gastrointestinal tuberculosis and the difficulties entailed in its diagnosis.

Epidemiology

The incidence of secondary intestinal tuberculosis varies with the severity of pulmonary disease. Of 3,693 cases examined roentgenographically, Williams found 626 (17%) positive for intestinal ulceration. Two percent of patients with minimal pulmonary disease, 8% with moderately advanced disease, and 25% with far-advanced disease had evidence of intestinal tuberculosis. An additional 485 patients had no pulmonary findings associated with their intestinal lesions (4). Mitchell and Bristol found that in a series of 5,529 tuberculous patients, 6.3% had enteric involvement, which correlated with the severity of pulmonary disease (5). They noted that the incidence of secondary intestinal tuberculosis fell from 10% to 1% of patients admitted to a tuberculosis sanitarium between 1924 and 1949.

Reports of primary intestinal tuberculosis, usually involving the ileocecal region, abounded until 1932 when the description by Crohn, Ginzburg, and Oppenheimer of regional ileitis as a distinct pathologic entity cast doubt on the existence of the condition (6). Many cases of intestinal granulomata, previously classified as tuberculous, lacked bacteriologic proof and were probably, in fact, cases of regional ileitis. The authors themselves claimed that the distinction was difficult to make and insisted on careful histologic and bacteriologic examination to prove the tuberculous etiology of ileocecal disease. In a retrospective study of 4,800 autopsies and surgical material, they identified only eight cases of ileocecal tuberculosis by histologic study (7).

In underdeveloped countries where tuberculosis continues to be a major health problem, abdominal disease occurs both as a result of pulmonary infection and, quite frequently, as the primary site. In Delhi, India, enteric tuberculosis comprises 0.8% of hospital admissions and is responsible for 3.4%–11% of cases of small-bowel obstruction (8, 9). In Iraq, it accounts for 2% of surgical admissions (10). In Ibadan, Nigeria, about 2.5% of hospital admissions are for abdominal tuberculosis (11). In recent years, an increasing number of reports of intestinal tuberculosis have come from Great Britain, primarily because of the influx of immigrants from the Indian

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TABLE 1

Manifestations Reported in Several Series

	Obstruction	Perforation	Chronic
Bhansali (8)*	32%	14%	44%
Das (3)	51%	0	49%
Vaidya (9)	61%	4%	35%
Mukerjee (39)	13% (all acute)	0	87%

* Percentages do not add up to 100%; 10% were other acute manifestations.

subcontinent (2, 12–17). Not surprisingly, the accuracy of preoperative diagnoses of intestinal tuberculosis corresponds to the prevalence of the disease. Even when clinical awareness is high, correct diagnoses rarely exceed 50% of cases (3, 11). In North America, the diagnostic failure rate is high, and scattered case reports emphasize the protean manifestations of tuberculous enteritis. (18–24).

Etiology

Historically, the description of intestinal tuberculosis as either primary or secondary reflected the presumed etiology of the disease (25). Secondary intestinal infection occurred when sputum infected with the human strain of *Mycobacterium tuberculosis* was swallowed and led to ulcerative enteritis. Primary infection resulted when the ingestion of milk contaminated with the bovine strain produced hyperplastic ileocecal tuberculosis. The decline in incidence of primary intestinal tuberculosis was thus attributed both to the pasteurization of milk and to the recognition of regional ileitis as a distinct clinical entity (7, 26). This reasoning has not been supported by Anand and Ukil in India, who reported that human-type bacilli were recovered in nearly all patients with isolated ileocecal tuberculosis (27, 28). More recent cases from Iraq, however, confirm the frequent occurrence of intestinal infestation with bovine strains (10), and isolates from cases in Belgium also demonstrate bovine bacilli (29).

The correlation between primary and secondary enteric infection and their particular morphologic features has also been inconsistent. Although most cases of hypertrophic ileocecal tuberculosis seem to occur without concomitant pulmonary infection (26, 27), reports of hypertrophic tuberculosis presumed secondary to pulmonary disease also exist (20, 30). Similarly, ulcerative enteritis has been reported in the absence of pulmonary involvement (31). Thus, it is unclear why the intestinal lesion produced by the bacilli is at times ulcerative and at other times hypertrophic or a combination of the two, i.e., ulcerohypertrophic (32). Virulence of the organism, the quantity ingested, and the immunologic response of the host may influence the morphology of the lesion.

Pathogenesis

Tubercle bacilli show special predilection for the ileocecal region, affecting it in 75%–90% of cases of tuberculous enteritis (33, 34). Rankine postulated four factors that lead to the localization of the lesion: the relative physiologic stasis of the area; the abundance of lymphoid tissue; the rapid rate of absorption at the region; the increased contact of bacilli with the intestinal mucosa because of the more completely digested small-bowel contents (35). Affected areas of the gastrointestinal tract are, in decreasing order of frequency: ileum (31%), cecum (21%), ascending colon (11%), transverse colon (7%), descending colon (7%), jejunum (6%), sigmoid colon (5%), rectum (2%), appendix (2%), and diffuse (8%) (34).

The organism penetrates the epithelial

TABLE 2

Symptomatology Reported by Several Authors

	Anand (27)	Bhansali (8)	Lewis (11)	Das (3)	Mukerjee (39)
Pain	100%	100%	90%	94%	100%
Loss of weight	76%	19%	90%	35%	80%
Anorexia	74%	—	62%	44%	95%
Weakness/fatigue	48%	—	—	—	—
Fever	58%	43%	75%	42%	83%
Nausea/vomiting	56%	66%	35%	70%	95%
Mass in abdomen	48%	24%	40%	29%	39%
Constipation	28%	41%	1%	47%	—
Diarrhea	22%	16%	34%	11%	10%
Constipation/diarrhea	8%	13%	—	9%	—
Amenorrhea	4%	11%	80%	36%	50%

TABLE 3

Laboratory Findings Reported in Several Series

	Anand (27)	Bhansali (8)	Lewis (11)	Das (3)	Mukerjee (39)
Elevated ESR	80%	—	—	93%	87%
Increased WBC	6%	—	36%	44%	—
Lymphocytosis	32%	—	26%	11%	—
Anemia	100%	Common	40%	88%	—
Positive CXR	22%	10%	—	15%	40%

lining of the intestinal mucosa and is carried by phagocytes to the submucosa where it initiates an inflammatory reaction in the lymphoid follicles of Peyer's patches. Endarteritis of the vessels of the overlying mucosa may lead to sloughing and formation of ulcers. Submucosal inflammation leads to thickening of the bowel wall with heavy cellular infiltration, edema, follicle formation, and, ultimately, as the ulcers heal, fibrosis. Invasion of mesenteric lymph nodes causes hyperplasia as well as caseation and necrosis. The lymph node histology shows caseous necrosis with epithelioid cells, giant cells of Langhans type surrounded by a peripheral zone of chronic inflammatory cells; the histology of the bowel wall may show only nonspecific inflammatory changes (25, 36).

The pathologic mechanism proposed above has been supported by experimental studies. Tuberculous bacilli were injected into the small intestine of dogs through a Thiry-Vella fistula, and then blood withdrawn at hourly intervals was used to inoculate guinea pigs (32). The animals contracted tuberculosis, demonstrating the permeability of the intestinal mucosa to the organism.

Retrograde lymphatic extension from nodes into the bowel wall and hematogenous spread have also been proposed as the initiating events in tuberculous enteritis, further obscuring the distinction between primary and secondary infection (36, 37). If retrograde lymphatic spread is accepted as a possible route of infection, then involvement of mesenteric nodes may precede involvement of the bowel wall. Quiescent mesenteric nodal infection has been invoked to explain the long latent periods between the arrival of Indian immigrants in England and the onset of symptoms (2, 12). Hematogenous spread may lead to seeding of the intestinal wall or peritoneum, which, if the primary pulmonary focus heals completely, may later give rise to seemingly isolated tuberculous enteritis or peritonitis (38).

Clinical Features

Numerous series have reported a preponderance of intestinal tuberculosis in women in the 3rd or 4th decade of life. Mukerjee and Singal assert that, especially in India, a mass in the right iliac fossa in a woman 20–40 years of age with a history of recurrent subacute obstruction indicates ileocecal tuberculosis until proven otherwise (39). The ratio of women to men is usually 2–3:1 (9, 11), although in British reports men predominate, probably reflecting the composition of the immigrant population (12, 16).

The presentation of abdominal tuberculosis can be either acute or chronic. Acute presentation occurs in 15%–65%, usually with intestinal obstruction or perforation (9, 39). Since some studies limit their consideration to intestinal tuberculosis and do not include tuberculous ascites or peritonitis, discordant findings are difficult to interpret. In a review of 50 or more patients, pain was reported as the most common symptom, followed by weight loss, anorexia, lassitude, intermittent fevers, and disturbance in bowel function. Amenorrhea or menstrual disturbances occurred in up to 80% of female patients. An abdominal mass, usually in the right iliac fossa, was present in up to half of the patients. Other symptoms and signs, encountered with lesser frequency, included distention, borborygmi, distress after meals, night sweats, and the presence of blood in the stool.

The duration of symptoms varied widely from less than three months to more than five years, with the majority of patients experiencing pain for 6–12 months (3, 8, 11, 27, 39).

Investigations

Laboratory investigations indicated the presence of chronic illness with a raised ESR and anemia. Leukocytosis was an inconstant finding, as was relative lymphocytosis.

Evidence of tuberculosis revealed by chest x-ray ranged from 11% to 40% (27).

Barium studies were helpful in localizing the pathology to the ileocecal region. The most common changes noted were filling defects in the cecum, shortening of the ascending colon, and dilation of the bowel proximal to the lesion. Nonfilling of the cecum and/or ascending colon in spite of normal filling of the terminal ileum and distal colon, indicating hypermotility of the area, constitute the so-called Stierlin's sign. This was originally described in 1911 as diagnostic of ileocecal tuberculosis (40) (see below).

The reported reactivity of patients with intestinal tuberculosis to tuberculin varied from 31% to 100% (2, 13, 16, 41–43). The reason for such a high incidence of nonreactivity is unclear: the Mantoux test is considered quite reliable in pulmonary infections, although it becomes negative in miliary or overwhelming infections. One may speculate that if the infectious focus is confined to the intestines, hematogenous spread has never occurred and systemic immunity has not been sufficiently stimulated. Caution should be used in interpreting positive results since in underdeveloped countries large portions of the healthy population react to tuberculin as a result of past exposure.

Diagnosis

The clinical and laboratory findings of abdominal tuberculosis lack specificity, and an operative procedure is often required to establish the diagnosis. Laparotomy may be performed, although, more recently, both laparoscopy and open peritoneal biopsy have been successfully used as accurate and less invasive methods of diagnosis (2, 3). Both may be particularly useful in patients with ascites or chronic miliary peritonitis (38). Colonoscopy has been used for diagnosis, especially in lesions suspicious for malignancy (56). The choice of the most appropriate diagnostic procedure will depend on the clinical pathology mimicked by the tuberculous lesion.

The diagnosis of enteric tuberculosis must be validated by histologic and bacteriologic study of tissue. Hoon et al proposed four diagnostic criteria: animal inoculation or culture, presence of tuberclelike bacilli on acid-fast stains of the tissue, histologic evidence of caseation, and typical gross description of operative findings supported by presence of caseation in mesenteric lymph nodes or peritoneal biopsy (32). Attempts to follow the criteria have not been uniformly successful (41, 44, 45). Histologic proof has been the easiest to obtain, often after a prolonged search through multiple tissue sections. Stewart first observed that caseating granulomata may appear solely in the regional lymph nodes; the bowel wall may show nonspecific inflammatory changes (25). Acid-fast stains provide a quick way of making a diagnosis, although the yield is limited (12, 32). Undoubtedly, bacteriologic culture and guinea pig inoculation offer the most conclusive methods of diagnosis, but they give positive results in less than half of the cases (27, 41). Numerous investigators have noted that the presence of caseation bears little relationship to positive cultures or to the ability to demonstrate bacilli on tissue stains. The poor correlation between histologic and bacteriologic findings may, as Wig et al warn, lead clinicians to omit tuberculosis as a diagnostic consideration when caseation is absent and the tissue is not cultured (41). Preoperative administration of antituberculous therapy may also obscure the diagnosis by changing the morphologic pattern to nonspecific chronic inflammation (27, 46).

Differential

The establishment of diagnostic criteria was prompted by the difficulties in differentiating ileocecal tuberculosis from a myriad of other diseases of malignant, inflammatory, or infectious etiology. The differential diagnosis of abdominal pain accompanied by a mass in the right iliac fossa and a general deterioration of health includes Crohn's regional ileitis, cecal malignancy, appendicular abscess, primary intestinal lymphoma, amebiasis, actinomycosis, histoplasmosis, sarcoidosis, and malabsorption syndromes (22, 42, 47).

Most challenging is the distinction of ileocecal tuberculosis from Crohn's ileitis, which it can mimic even in microscopic detail. Some authors have proposed that the two entities represent different grades of the same condition (48) or that Crohn's ileitis represents partially treated tuberculosis (27). Cell-wall-deficient organisms and nontuberculous types of mycobacteria have been implicated as the causative agents in inflammatory bowel disease (49).

The original description of Crohn's ileitis shows it to be a disease of young adults who are symptomatic from several months to a few years (6). Its prominent features include abdominal pain, fever, diarrhea, loss of weight, anemia, weakness, and obstructive symptoms (50). Operative findings of a matted mass in the ileocecal region, an increase in subserosal fat, stenotic bowel wall encroaching on the lumen with ulcerations, and enlarged mesenteric lymph nodes typify both enteric tuberculosis and Crohn's ileitis (46, 48). Tandon and Prakash summarized their macroscopic differences: anal lesions, fistulae, deep transmural fissures, and longitudinal ulcers are more common in Crohn's disease, while miliary serosal nodules, circumferential, transverse ulcers, and fibrosis of muscularis propria are more prominent in tuberculosis (46). Histologically, both conditions exhibit chronic inflammation with cellular infiltration and areas of fibrosis; submucosal edema is more pronounced in Crohn's disease than tuberculosis (2). Granulomata, the classic mark of tuberculosis, may occur in regional ileitis. Tuberculous granulomata tend to be large and confluent with central areas of caseation and a peripheral zone of inflammation. In ileitis, they are smaller and more discrete and rarely involve the lymph nodes (12, 46).

Radiologic examination of the bowel has been employed as a diagnostic aid in the differentiation between ileocecal tuberculosis and regional ileitis. Stierlin noted hypermotility of the ileocecal segment, indicated by nonvisualization of the area on a barium enema (40). Such a finding may confirm the diagnosis when the clinical presentation is inconclusive (51). His writing, however, antedates the first report of regional ileitis and thus may have included other granulomatous disease. Additional roentgenographic features of ileocecal tuberculosis include shortening of the ascending colon and cecum, and pulling up of the ileum so that the angle between the ileum and ascending colon becomes obtuse (52, 53). Mucosal irregularities with stiffening and thickening of mucosal folds, as well as cobblestoning with pseudopolyposis, have also been described (2, 44, 54). Calcification of mesenteric lymph nodes is highly suggestive that the lesion is tuberculous. These features are not pathognomonic of tuberculosis: inflammation induced by tuberculosis or Crohn's ileitis results in a similar mechanical effect that produces the same radiologic appearance (20, 42).

Ileocecal tuberculosis as well as tuberculosis of more distant colon segments may mimic carcinoma since both present with cachexia, alterations in bowel function, and obstructive symptoms. The radiologic finding of a colonic apple-core stricture or a cecal filling defect is nonspecific and may indicate either a malignancy or a tuberculous lesion (23, 24, 55, 56). In contrast to the age distribution of tuberculosis in underdeveloped countries, in North America the disease has become an affliction of the elderly, among whom malignant change is also more likely to occur (57, 58).

The diagnostic error occurs on the side of the more prevalent condition. In North America and Great Britain, tuberculomata are diagnosed preoperatively as regional ileitis or carcinoma: the patient may undergo unnecessary surgery or, more dangerously, receive steroids (13). In Third World countries, where Crohn's disease and cancer of the bowel appear less frequently, both diseases may be erroneously, and ineffectively, treated with antituberculous therapy.

Treatment

Before the advent of specific antimicrobial chemotherapy, isolated ileocecal tuberculosis had a better prognosis than pulmonary disease, for it was amenable to surgical resection. Early on, a bypass procedure with an ileotransverse colostomy was the most commonly performed operation, but it was later replaced by right hemicolectomy (15). Anand advocated a one-stage right hemicolectomy with an end-to-end anastomosis because it was a procedure of low mortality and morbidity which provided definitive cure of the disease (59). Once the use of antituberculous medications became more widespread, many supplemented the resection with medical therapy (15, 41). In disease limited to the ileocecum, some consider chemotherapy unnecessary, although recurrences have been reported without its use (12, 59). More recently, an attempt has been made to treat solely with antituberculous agents (22). Some reports suggest that the process of healing results in fibrosis, creating strictures, so that surgical intervention is required at a later time (5, 55). The addition of steroids to the antibiotic regimen has been proposed to decrease the incidence of stricture formation (16, 38).

Complications

Complications that necessitate surgical intervention include obstruction, perforation with abscess formation, free perforation with peritonitis, and, more rarely, hemorrhage or fistula formation (44, 60, 61). Stenosis of the bowel wall, impingement of enlarged mesenteric lymph nodes upon the lumen, and adhesions from fibrotic process comprise the mechanisms of obstruction (34, 42).

Summary

Improvement in sanitary conditions, milk pasteurization, and antituberculous medication have decreased the incidence of enteric tuberculosis in the United States, but the disease remains prevalent in underdeveloped countries. Diagnosis may be difficult, since intestinal tuberculosis may mimic Crohn's ileitis or cecal malignancy in clinical, radiologic, or even operative specimens.

Enteric tuberculosis affects young adults, women more frequently than men. Pain is the most common symptom, followed by weight loss, anorexia, lassitude, intermittent fevers, and disturbances in bowel function. The physical examination shows cachexia and, often, an abdominal mass. Barium enema reveals hypermotility of the affected segment with filling defects. Because clinical and laboratory findings are nonspecific, an exploratory laparotomy is frequently required. The diagnosis of tuberculous enteritis is substantiated by demonstrating caseation or acid fast bacilli on histologic section, or by culturing mycobacteria. Chemotherapy has become the mainstay of therapy for enteric tuberculosis, although surgery is performed for obstructive lesions.

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Student Corner

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Management of Abscess and Enterocutaneous Fistula in a Patient With Crohn's Disease: Case Report

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The formation of enterocutaneous fistulae and abscesses are relatively common in patients with Crohn's disease. Estimates of incidence range between 13% and 18% (1, 2). Both complications can be spontaneous but occur more frequently in patients with previous surgery (2, 3). The explanation for postsurgical complications of abscess and fistula is most likely related to the mechanism of fistula formation in Crohn's disease. The inflammatory process extends transmurally through the bowel wall at areas of deep fissures. The inflamed serosa subsequently becomes adherent to adjacent viscera or parietal peritoneum. If this extramural process remains localized it forms an abscess; if it ulcerates into a contiguous viscus or to the skin, it becomes a fistula (1, 4). Recurrent disease proximal to previous surgical anastomoses provides additional sites for fistula formation.

Abscesses commonly occur in conjunction with the formation of fistulae. Steinberg et al (2) reported that 7 of 10 patients with enterocutaneous fistulae had an associated abscess. Other studies have offered more conservative estimates ranging between 9% (5) and 30% (6) for abscesses occurring concomittantly with fistulae in patients with Crohn's disease.

The proper management of these abscesses and enterocutaneous fistulae is still in dispute. One group advocates early surgical intervention by resection of the diseased segment of bowel and excision of the fistulous tract (2, 7, 8). Others support the use of total parenteral nutrition (TPN) to achieve spontaneous closure of the fistula with resolution of the abscess cavity (9–12). A third group advocates the use of hyperalimentation for 30 to 40 days to achieve nutritional stability and then surgical resection for persistent unhealing fistulae (13–16).

The purpose of this paper is to examine the various therapeutic modalities employed in the treatment of abscess and enterocutaneous fistula in Crohn's disease, beginning with a case report that illustrates the inherent difficulties in diagnosis and management.

Case Report

A 52-year-old white woman had an 18-year history of Crohn's disease, originally diagnosed in 1965 following several episodes of severe diarrhea, weight loss, and malabsorption. A barium enema performed at that time revealed marked shortening of the left colon and a characteristic string sign of Kantor in the terminal ileum. She was initially treated with intramuscular cortisone and improved markedly. After several weeks, however, she developed an anaphylactic reaction to cortisone, and steroid therapy was subsequently discontinued. She was discharged without medications and remained asymptomatic during the following 13 years.

In 1978 she had a left lower quadrant abdominal, sausage-shaped tender mass. On admission, she was afebrile with normal blood indices. Ultrasonographic examination of the mass revealed an abdominal wall abscess. She was treated with intravenous cefazolin, and both the mass and the associated tenderness completely resolved.

One year later, she developed an identical

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mass in the same location, this time coupled with temperature spikes to 104°F which were refractory to intravenous cefazolin. An exploratory laparotomy was performed with the tentative diagnosis of recurrent Crohn's disease with abscess formation. Operative findings included the presence of matted adhesions between the left colon, loops of small bowel, omentum, and peritoneum. Because there was no evidence of suppuration, no other procedure was performed at this time. Postoperatively, the patient was started on a regimen of cefazolin, and her symptoms resolved. She was discharged after a relatively uneventful postoperative course.

The patient remained symptom-free for the next four years; two months prior to admission, the patient noticed a tender, left lower quadrant abdominal mass. The mass was ovoid and associated with crampy abdominal pain, diarrhea, and temperatures to 101°F, unrelieved by cefazolin. The patient self-administered 60 mg prednisone, and all symptoms transiently subsided. She tapered the prednisone dosage over the ensuing five weeks until at 15 mg the symptoms returned. Subsequent increases in dosage coupled with the administration of Vibramycin (3 tablets/day) failed to resolve her symptoms.

On admission, a large, tender, nonfluctuant swelling was palpated in the left lower quadrant of the abdomen. No signs of peritoneal inflammation were evident. As the patient was febrile (101°F) with marked leukocytosis and shift to the left (21,000 WBC, 32 bands), she was placed on intravenous antibiotics (cefoxitin 8 gm daily, ampicillin 4 gm daily). After five days, she defervesced and her blood indices returned to normal.

Ultrasonography of the abdomen demonstrated a large abscess measuring 11 cm, 6.5 cm thick in the left flank, extending into the extraperitoneal fat space and abdominal wall musculature. Barium enema performed on the fifth hospital day demonstrated marked narrowing and shortening of the transverse colon, as well as inflammatory changes typical of Crohn's disease in the right colon and cecum. Numerous sinus tracks extending into the mesentery were also noted. Computerized axial tomography performed three days later confirmed the sonography results. In addition, residual barium was present in the abscess cavity, indicating an enteric communication. Colonoscopy and biopsy samples confirmed previous findings of active Crohn's disease, marked by nodularity and cobblestone mucosal deformities in the transverse and descending colon. A sinus opening was also visualized in the left colon.

On the thirteenth hospital day, surgical drainage of the abscess was performed. Approximately 600 ml of odorous, purulent material was removed. Following blunt dissection and breakdown of existing loculations, the wound was carefully debrided and packed with moist surgical gauze. A Penrose drain was left in place to facilitate adequate drainage. Postoperatively, the patient was placed on a regimen of cefoxitin (8 gm daily) and ampicillin (4 gm daily). Local and systemic conditions improved, and she was discharged on the eighth postoperative day with minimal but persistent drainage. At the time of submission of this paper two months later, the wound had not healed and was continuing to drain a purulent, foul-smelling material. In addition, the patient complained of the frequent passage of gas from the open wound. Future definitive treatment consisting of resection of the diseased bowel and fistulous tract has been suggested.

Discussion

Several aspects of this case are worthy of note. The diagnosis of abscess with concurrent fistula is often difficult to make, especially if the fistula is of the low output variety described by several authors (13, 17). In this case, the external opening was not readily apparent, even after surgical drainage of the abscess cavity. The continuity between the bowel lumen and the abscess was demonstrated radiologically by the presence of barium in the abscess cavity several days after barium studies had been performed on the lower gastrointestinal tract. Subsequent colonoscopy confirmed the fistulous opening. Several series have pointed out the not uncommon finding of abscess associated with enterocutaneous fistulae (5, 6). Steinberg et al (2) suggest that both conditions are part of the same pathologic process of slow penetration of the intestinal wall by a fissure ulcer.

The spontaneous formation of enterocutaneous fistulae is not uncommon in inflammatory bowel disease (18). In studies of all patients with external GI fistulae, Crohn's disease has been implicated as the major cause of spontaneous fistulization (19). Tracts communicating with the umbilicus are the most frequently reported sites in spontaneous fistula formation (2, 4). Hiley et al (20) studied four patients with spontaneous umbilical fistulae. In two cases, the formation of the coloumbilical fistula was preceded by a precolic intraabdominal abscess. They suggested that the urachal remnants provided the path of least resistance for the spread of the inflammatory process between contiguous structures.

Several groups have suggested that surgical complications or anastomotic breakdown account for most external fistulae of the GI tract (3, 19). Other series indicate that the majority are the result of recurrent disease and not a direct complication of surgery (2). Greenstein et al (1) described 20 patients who developed external fistulae after surgical intervention. The occurrence of postoperative fistulae was not procedure-specific; some followed bypass and resection, others followed appendectomy or simple laparotomy. Other studies indicate that a persistent enterocutaneous fistula almost always follows simple drainage of superficial and deep abscesses (2).

Determining the etiology of the fistula has important implications for management. Postoperative fistulae occurring without radiologic evidence of active or residual Crohn's disease or distal obstruction usually heal spontaneously or with medical treatment alone (8). Conversely, fistulae associated with radiologically confirmed active disease require more extensive therapy, including parenteral nutrition and surgery to induce closure (8–10).

Although management of enterocutaneous fistulae in conditions other than inflammatory bowel disease is well described, studies describing treatment in patients suffering from Crohn's disease are few (8). The importance of management is underscored by the results of a study conducted by Farmer et al (21), which demonstrated that 32% of all surgery in Crohn's disease was related to the complications of fistula and abscess formation. Other series have indicated increased surgical intervention in patients with fistulae (1).

Medical vs Surgical Management. Certain principals of management, including the treatment of sepsis, nutritional and metabolic support, skin care, and surgical intervention to relieve distal obstruction (5, 8, 13, 22), are fundamental to all methods of treatment, and will not be discussed further here. More important is the dichotomy of opinion on the efficacy of medical versus surgical management.

Several authors report good success rates with medical management alone (9, 11, 12, 23). Medical management includes total parenteral nutrition (TPN) and antibiotics to achieve spontaneous closure. Solutions frequently used for this purpose are protein hydrolysates, synthetic amino acid protein sources and dextrose (Freamine), and lipid and glucose mixtures (Intralipid) (19). Of historical note is the work of Chapman et al (24), which emphasized the importance of nutritional status in management. Patients who received more than 2,000 calories/day had a mortality rate of 16% compared to 58% in patients who received less than 1,000 calories/day.

The aim of TPN is to deliver 2,000–4,000 calories/day to the patient. This treatment has resulted in restoration of fluid and electrolyte balance, weight gain, a positive nitrogen balance, increased albumin-to-globulin ratios, and decreased fistula secretions (19). Increased spontaneous closure rates and decreased mortality rates have also been reported (11, 12).

MacFadyen and co-workers (11) studied 19 patients with Crohn's disease and reported a 40% spontaneous closure rate in patients managed with TPN alone. In these patients with Crohn's disease, the fistulae closed in an average of 26.8 days, compared to an average of 34.9 days for all patients studied. Other series have indicated that parenteral nutrition and bowel rest can induce spontaneous closure in up to 50% of enterocutaneous fistulae (9, 12, 23). One problem with these studies, however, is their failure to comment upon the respective recurrence rates of fistula formation in patients managed with TPN alone; for this reason the results of these studies are not widely accepted (13, 25).

Advocates of parenteral nutrition in the management of all patients with enterocutaneous fistulae often point out that spontaneous closure is much less likely to occur in patients with Crohn's disease, as well as in patients with malignancies or previous abdominal radiation (5, 13). Other authors have implicated distal obstruction, foreign bodies, and epithelialization of the fistulous tract as relative indications for operative intervention (17, 19). Despite these reports, TPN may still have efficacy in the initial treatment of external GI fistulae in patients with Crohn's disease. TPN can help to restore nitrogen balance as well as to correct fluid and electrolyte abnormalities (26), facilitating adequate preparation of the patient for surgery. In addition to the value of nutritional support, the infusion of glucose and amino acids has been shown to result in a 50% reduction in upper GI secretions (27). Decreased liquid passage through the fistula may facilitate closure of the tract.

The operative management of abscess and fistula involves diverse approaches, including superficial drainage of abscesses, curettage and simple suture (primary closure), proximal diverting ileostomy, and intestinal bypass procedures (2). More extensive surgery entails en bloc

TABLE

Management of Abscess and Enterocutaneous Fistula in Series of Patients with Crohn's Disease

Author/Date	No. pts.	Procedure	Closure (%)	Total mortality (%)
Enker 1969	10	Resection	90	NA
Lorenzo 1969	4	NA	NA	NA
MacFadyen 1973	19	TPN	40	5
Steinberg 1973	60	Primary	0	6
		closure, resection	84	NA
Aguirre 1974	7	TPN,	0	0
		resection	NA	NA
Greenstein 1974	108	Bypass,	50	NA
		resection	88	NA
Farmer 1976	169	Resection	NA	NA
Graham 1977	4	TPN	100	0
Driscol 1978	11	TPN,	9	0
		resection	100	0
Reber 1978	12	TPN	8	17
Sternquist 1978	4	TPN (1),	0	0
		resection (3)	100	0
Soeters 1979	20	TPN,	5	5
		resection	90	0
Fitzgibbon 1980	2	Resection	100	0
Rajah 1980	1	TPN × 6 wks	0	0
		resection	100	0
Broe 1982	12	Resection	NA	NA
Hawker 1983	39	TPN,	26	
		drainage,	13	3
		resection	97	
Zera 1983	9	TPN	0	NA

NA, not available.

resection of the affected segment of bowel along with the fistulous tract (2, 7, 8, 16).

Steinberg and co-workers (2) attempted simple drainage of 33 abdominal wall abscesses. A persistent fistula subsequently developed in 28 cases (85%). Other series report similarly high recurrence rates (1, 8). One explanation for these poor results may be that many of the abscesses pointing to the skin undoubtedly represent superficial extensions of deep abscesses (2). Drainage procedures lead to the formation of external fistulas which will rarely undergo spontaneous closure, but more often persist as a permanent fistulous tract until the major source of disease is eradicated (2). Simple drainage may be effective as part of a staged procedure in a severely septic patient. Early control of infection combined with metabolic support will prepare the patient for subsequent definitive surgery.

Bypass procedures have achieved only slightly better results than simple drainage (2). Such procedures, initially described by Edmunds et al (28), are not recommended, because they do not remove the underlying disease and usually require more than one suture line. In these cases, the fistula may fail to heal. The potential deterioration of the new anastomotic suture lines provides a site for de novo fistula formation (5). In cases where extensive disease precludes the establishment of intestinal continuity, Goligher (29) recommends excision of the bowel segment containing the fistula, bringing the proximal end to the surface as a stoma, and creating a mucus fistula of the distal end. This procedure may be more appropriate for fistulae with copious drainage than for those extruding minimal secretions.

Postoperative enterocutaneous fistulae more frequently arise following simple drainage of abscesses than following bypass procedures. Conversely, fistulae more commonly recur following bypass procedures than resections (7, 30). Estimates of postoperative fistula recurrence subsequent to bypass procedures range between 15% (31) and 50% (2); reported recurrences following resection vary between 5% (2) and 12.5% (1). From these studies, it is apparent that fistulae are more frequent sequellae to bypass procedures than to definitive surgical resection.

Most current studies indicate that the best results have been achieved with en bloc resection of the fistulous tract in continuity with the diseased bowel (Table). Steinberg et al (2) report a closure rate of 84% following a policy of excision surgery for Crohn's fistulae. Other series have obtained similar or better results (7, 8, 10, 22, 32, 33). Surgical treatment affords the opportunity to remove other sites of active or residual disease in addition to excision of the initial site of serosal inflammation and the narrow fibrosed segment often located distal to the fistula (2). Distal obstruction has been implicated as a cause of poor healing and recurrent fistula formation (14, 16, 19, 24). Surgical intervention therefore has a twofold purpose: actual excision of the primary source of the fistula and resection of other diseased segments of bowel.

Summary

The proper management of abscess and enterocutaneous fistula in patients with Crohn's disease is disputed. A successful approach to external GI fistulae should initially include TPN, fluid and electrolyte control, adequate skin protection, and prophylactic antibiotics (15). The increased caloric demands due to sepsis, and loss of protein-rich fluids and electrolytes, must be addressed before surgical intervention. Nutritional support maintains the integrity of the immune system and facilitates the healing of wounds (13). Malnutrition and sepsis have been implicated as predominant factors for failure in treatment (26, 34).

Previous studies suggest that TPN does not result in permanent closure of external GI fistulae in Crohn's disease (10). Therefore, after a 30-to-40-day course of parenteral nutrition, operative closure should be performed. Because 90% of all fistulae that close spontaneously do so within one month after infection has subsided, surgical closure should be performed for fistulae that persist beyond that time (13). Clearly the most efficacious operation is en bloc excision of the fistulous tract and segmental resection of the diseased bowel, including any distally obstructed segments, combined with end-to-end anastomosis. This combined policy of initial TPN and antibiotic therapy to correct nutritional imbalances and sepsis, followed by definitive surgical resection, is the most effective means of decreasing postoperative complications and mortality, while rapidly restoring the patient to good health.

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Indications and usage:
Sandimmune (cyclosporine) Oral Solution and I.V. are indicated for the prophylaxis of organ rejection in kidney, liver and heart allogeneic transplants. They are always to be used with adrenal corticosteroids. The drug may also be used in the treatment of chronic rejection in patients previously treated with other immunosuppressive agents.

Contraindications:
Hypersensitivity to cyclosporine and/or Cremophor® EL.

Warnings:
Nephrotoxicity has been noted in 25% of cases of renal transplantation, 38% of cases of cardiac transplantation and 37% of cases of liver transplantation. Mild nephrotoxicity was generally noted in two or three months after transplant and consisted of an arrest in the fall of the pre-operative elevations of BUN and creatinine at a range of 35-45 mg/dl and 2.0-2.5 mg/dl respectively. These elevations are often responsive to dosage reduction.

More overt nephrotoxicity was seen early after transplantation and was characterized by a rapidly rising BUN and creatinine. Since these events are similar to rejection episodes, care must be taken to differentiate between them. This form of nephrotoxicity is usually responsive to Sandimmune (cyclosporine) dosage reduction.

Impaired renal function at any time requires close monitoring, and frequent dosage adjustments may be indicated. In patients with persistent high elevations of BUN and creatinine who are unresponsive to dosage adjustments, consideration should be given to switching to other immunosuppressive therapy. In the event of severe and unremitting rejection, it is preferable to allow the kidney transplant to be rejected and removed rather than increase the Sandimmune (cyclosporine) dosage to a very high level in an attempt to reverse the rejection. Occasionally patients have developed a syndrome of thrombocytopenia and microangiopathic hemolytic anemia which may result in graft failure. Neither the pathogenesis nor the management of this syndrome is clear. Significant hyperkalemia and hyperuricemia have been seen occasionally in individual patients.

Hepatotoxicity has been noted in 4% of cases of renal transplantation, 7% of cases of cardiac transplantation and 4% of cases of liver transplantation. This was usually noted during the first month of therapy when high doses of Sandimmune (cyclosporine) were used and consisted of elevations of hepatic enzymes and bilirubin. The chemistry elevations usually decreased with a reduction of dosage.

Lymphomas have developed in patients receiving Sandimmune (cyclosporine) and other forms of immunosuppressive therapy after transplantation though no causal relationship has been established. With Sandimmune (cyclosporine), some patients have developed a lymphoproliferative disorder which regresses when the drug is discontinued.

There have been reports of convulsions in adult and pediatric patients receiving cyclosporine, particularly in combination with high dose methylprednisolone.

Rarely, patients receiving Sandimmune (cyclosporine) I.V. have experienced anaphylactic reactions believed due to the Cremophor EL (polyoxyethylated castor oil) used as the vehicle for the I.V. formulation and not found in the oral solution, the use of which has not been associated with anaphylactic reactions. **Patients receiving Sandimmune® (cyclosporine) I.V. should be under continuous observation for at least 30 minutes following the start of the infusion and at frequent intervals thereafter. If anaphylaxis occurs, the infusion should be stopped; and epinephrine and oxygen should be available at the bedside.**

Precautions:
General. Patients with malabsorption may have difficulty in achieving therapeutic levels with the oral solution. Given its hyperkalemic effect, cyclosporine should not be used concomitantly with potassium-sparing diuretics. In some patients with cardiac transplantation antihypertensive therapy was required.

Laboratory Tests: Renal and liver functions should be assessed repeatedly by measurement of BUN, serum creatinine, serum bilirubin and liver enzymes.

Drug Interactions: Care should be taken using Sandimmune (cyclosporine) with nephrotoxic drugs since potential synergies of nephrotoxicity may occur. Concurrent administration of rifampin, phenytoin, phenobarbital and I.V. sulfatrimethoprim may decrease plasma levels of cyclosporine. High dose methylprednisolone, erythromycin, ketoconazole, and amphotericin B may increase the plasma concentration of cyclosporine. Monitoring of plasma or blood levels of cyclosporine are essential when these drugs are used concomitantly.

Carcinogenesis, Mutagenesis and Impairment of Fertility. Cyclosporine gave no evidence of mutagenic or teratogenic effects in appropriate test systems. Only at dose levels toxic to dams, were adverse effects seen in reproduction studies in rats. (See Pregnancy.)

Carcinogenicity studies were carried out in both male and female rats and mice. In the 78 week mouse study, a statistically significant trend for lymphocytic lymphomas in females was found, and the occurrence of hepatocellular carcinomas in males receiving 4 mg/kg/day was significant. In a 24 month study, the occurrence of pancreatic islet cell adenomas in rats receiving 0.5 mg/kg/day was significant. The hepatocellular carcinomas and the pancreatic islet cell adenomas were not dose related.

No impairment in fertility was demonstrated in long-term studies in male and female rats.

Pregnancy: Pregnancy Category C. Sandimmune (cyclosporine) Oral Solution has been shown to be embryo- and fetotoxic in rats and rabbits when given in doses 2-5 times the human dose.

There are no adequate and well-controlled studies in pregnant women. Sandimmune (cyclosporine) should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: Since Sandimmune (cyclosporine) is excreted in human milk, nursing should be avoided.

Pediatric Use. Although no adequate and well-controlled studies have been conducted in children, patients as young as 6 months of age have received the drug with no unusual adverse effects.

Adverse reactions:
The principal adverse reactions to Sandimmune therapy are hirsutism, tremor, renal dysfunction, hypertension, and gum hyperplasia.

The following reactions occurred in 3% or greater of 892 patients involved in clinical trials of kidney, heart and liver transplants: renal dysfunction, hypertension, cramps, hirsutism, acne, tremor, convulsions, headache, gum hyperplasia, diarrhea, nausea/vomiting, hepatotoxicity, abdominal discomfort, paresthesia, flushing, leukopenia, lymphoma, sinusitis, gynecomastia.

The following reactions occurred in 2% or less of patients: allergic reactions, anemia, anorexia, confusion, conjunctivitis, edema, fever, brittle fingernails, gastritis, hearing loss, hiccups, hyperglycemia, muscle pain, peptic ulcer, thrombocytopenia, tinnitus.

The following reactions occurred rarely: anxiety, chest pain, constipation, depression, hair breaking, hematuria, joint pain, lethargy, mouth sores, myocardial infarction, night sweats, pancreatitis, pruritus, swallowing difficulty, tingling, upper GI bleeding, visual disturbance, weakness, weight loss.

Blood Level Monitoring: Several study centers have found blood level monitoring of cyclosporine useful in patient management. While no fixed relationships have yet been established, 24 hour trough values of 250-800 ng/ml (whole blood, RIA) or 50-300 ng/ml (plasma, RIA) appear to minimize side effects and rejection events.

How supplied:
Sandimmune (cyclosporine) Oral Solution —
50 ml bottles containing 100 mg/ml of cyclosporine
Sandimmune (cyclosporine) I.V. —
5 ml ampuls containing 50 mg/ml of cyclosporine. (SDI-Z5-6/15/85)

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Diagnosis of Cyclosporine Nephrotoxicity

J. R. Salaman, M.Ch., FRCS

Since its introduction in 1978 by Calne et al. (1), cyclosporine has been adopted by most transplantation centers because of the clear benefit it has brought to clinical transplantation. Rejection has been more effectively and safely suppressed and patient and graft survival rates have, as a consequence, improved dramatically. Nonetheless, the nephrotoxicity that cyclosporine can induce has been a cause of concern and confusion and has made the management of cyclosporine-treated patients quite difficult. Nephrotoxicity has been observed not only in recipients of kidney transplants but also in recipients of bone marrow and other organ transplants and in patients who have received cyclosporine for treatment of autoimmune disease. This nephrotoxicity appears to be reversible, and renal function usually improves rapidly when the dose of cyclosporine is reduced. There has been concern that nephrotoxicity might proceed to permanent renal damage (2, 3). This now seems unlikely provided the maintenance cyclosporine dose does not exceed 10 mg/kg per day (4).

Diagnosis of Nephrotoxicity. In kidney transplantation the impairment of renal function caused by cyclosporine can be difficult to differentiate from rejection and other causes of poor kidney function. The classical feature of toxicity is a rise in the serum creatinine and urea concentrations in the presence of maintained urine output. Usually the creatinine rise is greater than the urea rise, and there is often an inappropriate increase in the serum potassium concentration as well. Unfortunately, these features are not unique to nephrotoxicity; what is more, nephrotoxicity can occur in the presence of rejection or acute tubular necrosis.

In attempting to differentiate nephrotoxicity from rejection, a variety of maneuvers have been tried. Perhaps the simplest has been to reduce the dose of cyclosporine and see if renal function has improved by the following day. Most episodes of renal impairment can be managed in this way. If the diagnosis ultimately proves to be rejection, then I do not believe any harm will have been done, for there is no evidence that a 24-hour delay in treating rejection compromises long-term survival.

Monitoring cyclosporine blood levels may be of some help, and if a whole-blood cyclosporine level of 800 ng/ml or more is recorded, nephrotoxicity is the most likely diagnosis. Patients appear to vary in susceptibility to nephrotoxicity. Some can tolerate very high blood cyclosporine levels, whereas others will develop nephrotoxicity with levels of 300 ng/ml or less.

Renal biopsy is commonly performed in renal transplant centers but has not helped to any great extent in differentiating nephrotoxicity from rejection. Nonetheless, in the presence of cyclosporine toxicity, a lymphoid infiltrate, if present, is often focal in distribution rather than diffuse, as may be seen with rejection. In addition, the arterioles may show hyalinosis and hypertrophy if there is nephrotoxicity, whereas rejecting kidneys usually display endothelial cell proliferation (5). It has been suggested that long-standing nephrotoxicity will induce interstitial fibrosis (3), but this has not been confirmed by others, and where groups of patients have been compared, interstitial fibrosis has been no commoner in patients treated with cyclosporine than in those immunosuppressed with azathioprine (6).

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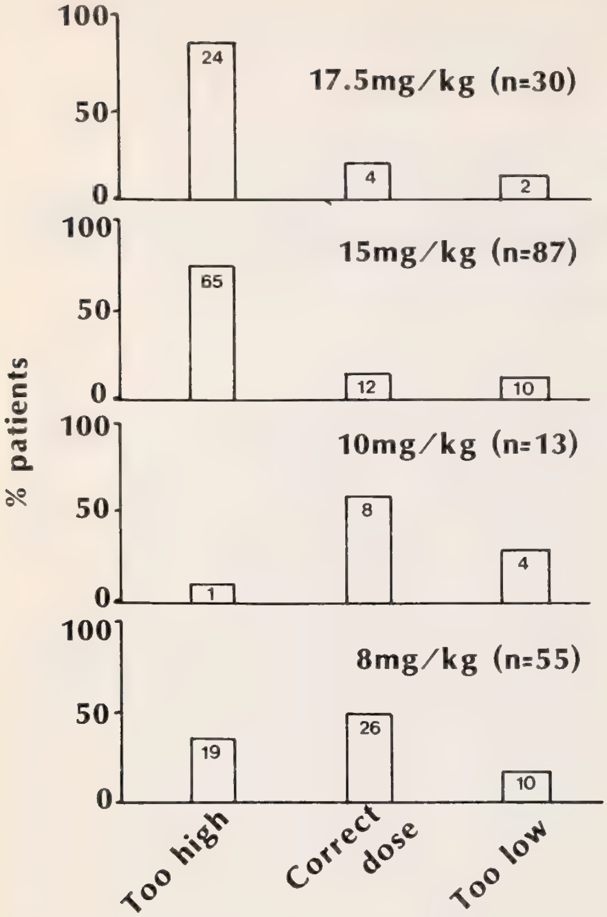

Fig. Comparison of four different cyclosporine protocols in kidney transplantation showing proportion of patients who required a dose reduction in first month because of toxicity, or who required larger dose because of low cyclosporine blood levels and rejection. Starting doses ranged from 8 to 17 mg/kg per day. Optimum dose seems to be 8–10 mg/kg per day.

Fine-needle aspiration cytology has also been used to differentiate nephrotoxicity from rejection. Actual deposits of cyclosporine can be demonstrated by indirect immunofluorescence in aspirates from kidneys experiencing toxicity (7). In the presence of rejection, the aspirates will contain many inflammatory cells (8). The drawback of this method is that the identification of the various cell types is difficult, even by an experienced cytologist.

Measuring intrarenal pressure is another method that has been used to differentiate nephrotoxicity from rejection. This test can be performed at the patient's bedside. It involves passing a fine-gauge needle into the transplant and connecting the needle to an air pressure manometer (9). In most cases of rejection the pressure rises above 40 mm Hg but in the presence of cyclosporine nephrotoxicity it remains in the normal range (27 ± 12 mm Hg). We have shown that this test can be most useful in the management of cyclosporine-treated patients (10), and this has been confirmed by others (11–13). Unfortunately, chronic vascular rejection may not cause the intrarenal pressure to rise, and therefore this test tends to lose its value the longer the time after transplantation (14).

Factors Contributing to Nephrotoxicity. To a large extent cyclosporine nephrotoxicity is avoidable. The starting dose originally chosen by Calne et al (1) was 17 mg/kg per day, but it has since been found that this is too high and most transplant centers have moved to a dose that is somewhat lower. Since 1982 we have used cyclosporine in four different protocols at starting doses ranging from 8 to 17 mg/kg per day. The proportion of patients whose dose had to be reduced during the first month because of nephrotoxicity is shown in Fig. The proportion for whom the starting dose was too low, giving unsatisfactory blood levels, is also shown, and it can be seen that a dose of 10 mg/kg is probably best. Even at 8 mg/kg per day some patients still developed nephrotoxicity, and there is undoubtedly great variation among patients in susceptibility to this complication.

A number of medications can increase the nephrotoxic effect of cyclosporine if given concurrently. In some cases this is due to the drugs acting together on the renal tubular cells; this group includes such agents as aminoglycosides, amphotericin, co-trimoxazole, trimethoprim, and melphalan (15). With other drugs it seems that the nephrotoxicity is due to a rise in cyclosporine blood levels brought about through reduced hepatic metabolism. Examples of these agents are ketoconazole, cimetidine, oral contraceptives, erythromycin, danazol, and norethisterone (15).

The effect of steroids on cyclosporine metabolism is somewhat complex. High doses of methylprednisolone can increase cyclosporine blood levels by competing for metabolism in the liver via the cytochrome P-450 pathway. Low maintenance doses of steroids seem to have the opposite effect, and we have noted that cyclosporine nephrotoxicity is significantly less common in patients who take maintenance steroids than in those receiving cyclosporine alone (16).

Avoidance of Nephrotoxicity. Nephrotoxicity is an unwelcome complication of cyclosporine treatment but may be managed relatively easily. It can be largely avoided if the starting dose of cyclosporine is about 10 mg/kg per day and if blood levels are monitored regularly, especially during the first few months. Clearly, drugs that interact with cyclosporine should be avoided whenever possible, or the dose of cyclosporine should be reduced appropriately. It would seem sensible to inform family doctors of these interactions. We have found that when family doctors have prescribed certain medications, such as antibiotics, this has not infrequently resulted in raised creatinine values, which can easily be mistaken for rejection.

Summary. Nephrotoxicity is a troublesome complication of cyclosporine therapy, although it appears that long-term damage to the kidney is unlikely if high doses of cyclosporine can be avoided. The diagnosis of nephrotoxicity is usually based on increased serum levels of creatinine and potassium and is confirmed by noting a fall in these values when the dose of cyclosporine is reduced. Cyclosporine blood levels as well as needle biopsy, fine-needle aspiration cytology, and fine-needle intrarenal manometry may be helpful in making the diagnosis. Significant nephrotoxicity is uncommon when the starting dose of cyclosporine is 10 mg/kg per day or less and when care is taken to avoid concomitant administration of drugs known to increase the nephrotoxic effect.

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Cyclosporine and Oncogenesis

ISRAEL PENN, M.D.

Abstract

Cancers developed in 130 organ transplant recipients treated with cyclosporine. The malignancies showed important differences from those seen following conventional immunosuppressive therapy. Tumors appeared an average of 20 months after cyclosporine and 60 months after conventional therapy. Non-Hodgkin lymphomas were the most common neoplasms, occurring in 43% of cyclosporine-treated patients compared to 12% of conventionally treated patients. These lymphomas appeared an average of 11 months after transplantation, compared to an average of 42 months after conventional therapy. In cyclosporine-treated patients the lymphomas more often involved lymph nodes, more frequently involved the small intestine, rarely involved the brain, and were more likely to regress after reduction of immunosuppressive therapy. Skin cancers (16% of cancers) were much less common than in conventionally treated patients (40%); Kaposi's sarcoma was more common (8% versus 3%). In this small series there was a surprising frequency of endocrine-related malignancies and renal cell carcinomas. Only seven (5%) of the patients were treated with cyclosporine exclusively. The cancers probably are not specific to cyclosporine therapy but appear to be a complication of immunosuppression.

After early clinical trials with cyclosporine, 3 of 34 transplant recipients (9%) developed lymphomas (1). Further experience with the drug reduced the anxiety generated by this data; the incidence of lymphomas and lymphoproliferative disorders was found to be 0.4% in approximately 5,550 transplant patients treated with cyclosporine alone or together with low-dose steroids (2). The purpose of this study is to analyze the types of tumors that have occurred after administration of cyclosporine and to compare them with the neoplasms that have developed after conventional immunosuppressive therapy.

Clinical Data

Up to March 1986, the Cincinnati Transplant Tumor Registry (CTTR) had received data on 2,696 cancers that developed after transplantation in 2,521 organ transplant recipients (2–6). Of these patients, 130 developed 131 tumors after cyclosporine therapy. There were no differences in average age (40 years) or sex distribution (2:1 male–female ratio) between the patients given cyclosporine and those treated with conventional immunosuppressive therapy.

The average time of appearance of the neoplasms after conventional therapy was 60 months (range 1–244.5). In striking contrast, malignancies that followed cyclosporine administration occurred very early after transplantation, at an average of only 20 months (range 1–233.5). Several patients at the late end of the time range either had been switched from conventional therapy to cyclosporine or had received conventional therapy with a first transplant and cyclosporine with a subsequent transplant. Of the 130

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patients, 11 received two transplants and 2 had three transplants. It must be emphasized that only 7 of the 130 patients (5%) who developed tumors following cyclosporine therapy were treated exclusively with this agent. Other immunosuppressive agents and treatments used included prednisone or related compounds (122), azathioprine (56), antilymphocyte globulin (39), splenectomy (8), thoracic duct fistula (4), local radiation to the graft (3), total-body irradiation (2), cyclophosphamide (2), and cytimun (1).

Cancers after cyclosporine therapy occurred particularly among recipients of extrarenal organs. Although 96 of the patients who developed cancers were renal transplant recipients, they constituted only 4% of such recipients in the CTTR. Others were 15 heart recipients (28% of CTTR total), 7 liver recipients (78% of CTTR total), 5 pancreas recipients (83% of CTTR total), 5 bone marrow recipients (36% of CTTR total), and 2 combined heart and lung recipients (100% of CTTR total). Most of the malignancies that occurred in recipients of extrarenal organs (26 of 34, or 76%) were lymphomas. In fact, 26 of the 56 patients (46%) in this series who developed lymphomas had received extrarenal organs.

The tumors that developed following cyclosporine therapy (Table 1) differed in several ways from the tumors that developed following conventional therapy (Table 2). Lymphomas constituted 43% of cyclosporine-related tumors, compared to 12% of tumors following conventional treatment. Similarly, Kaposi's sarcomas were more frequent in the cyclosporine group (8 versus 3%). Conversely, skin cancers and in situ uterine cervical carcinomas were more frequent in the conventional treatment group. No carcinomas of the vulva or perineum have thus far been encountered in the cyclosporine-treated patients, whereas they made up 3% of tumors in conventionally treated patients.

Lymphomas. In the cyclosporine group, lymphomas appeared a remarkably short time after transplantation, at an average of 11 months (range 1–68) compared to an average of 42 months (range 1–190.5) after conventional therapy. The types of lymphomas were similar to those seen after conventional immunosuppression. All were non-Hodgkin lymphomas (NHLs); 18 were classified as reticulum cell sarcomas or large cell lymphomas or immunoblastomas, 19 as B-cell lymphomas, 7 as B-cell hyperplasias, probably lymphomas. There were no cases of Hodgkin's disease, multiple myeloma, or T-cell lymphoma, small numbers of which occurred in the conventionally treated group. In both the cyclosporine-treated and the conventionally immunosuppressed patients there is strong suggestive evidence that Epstein-Barr virus played an etiological role in some NHLs.

The cyclosporine-related NHLs were similar to those that occurred following conventional immunosuppression in that they frequently involved lymph nodes, liver, spleen, bone marrow, lungs, small intestine, and the allografts (mainly renal). However, there were several important differences in the distribution of the lesions. In the general population 52–76% of NHLs involve lymph nodes and 24–48% are extranodal (6). In the conventional therapy group the great majority (78%) were extranodal and only 22% were nodal. The cyclosporine group more closely resembled the general population in that 46% of the NHLs were nodal and 54% extranodal. Small-bowel involvement occurred in 33 of 292 NHLs (11%) in the conventionally treated group but in 16 of 56 (29%) in the cyclosporine-treated group. The disease was localized to the small bowel in only 15% of the former group but in 44% of the latter. A striking feature of NHLs in the conventional therapy group was frequent involvement of the central nervous system, which occurred in 117 of 292 patients (40%) (4, 6). Of these, 88 (75%) of the NHLs were confined to the central nervous system. In contrast, only 2 of 56 (4%) NHLs in the cyclosporine group affected the central nervous system, and both occurred in patients with widespread lymphomas.

Calculations have shown a 48-fold increase in mortality from lymphomas in conventionally treated transplant patients (7). Non-Hodgkin lymphomas in the cyclosporine group appeared to respond more readily to treatment than those in the conventional therapy group. In 25 of the 56 cyclosporine-treated patients (45%) there was complete regression of the lesions following various treatments, including reduction or cessation of immunosuppressive therapy, surgical excision, administration of acyclovir, radiation therapy, and chemotherapy. Four of the remissions occurred when the only treatment was reduction or cessation of the immunosuppressive therapy. The great majority of the remissions occurred in patients whose disease was localized to a single viscus.

Skin Cancers. Of the cyclosporine-treated patients, 13 had squamous cell carcinomas and 8 had basal cell carcinomas. This is similar to the pattern seen in conventionally treated patients, where squamous cell outnumber basal cell carci-

TABLE 1

Neoplasms Following Cyclosporine Therapy

Tumor type or site	No. of cases
Lymphoma	56
Skin	21*
Kaposi's sarcoma	11
lung	6
kidney	5
breast	5
testis	3†
Unknown primary	3
colon	3*
cervix	3
larynx/nasopharynx	3
ovary	2
thyroid	1
pancreas	1
Spindle cell sarcoma of bile duct	1
Neuroectodermal brain tumor	1
prostate	1
vagina	1
Chronic myeloid leukemia	1
Carcinoid tumor	1
bladder	1
stomach	1

* One patient had carcinoma of colon and basal cell carcinoma of skin.

† One occurred in the intraabdominal gonad of a hermaphrodite.

nomas, but the reverse of the situation in the general population (4, 6). No malignant melanomas have been seen in the cyclosporine-treated patients, whereas they constitute 4.9% of skin cancers in conventionally treated patients.

Kaposi's Sarcoma. The inordinately high incidence of Kaposi's sarcoma should be noted again. Three patients had visceral disease, 1 had lymph node involvement, and 7 had skin lesions only. The distribution of the lesions and the behavior of the neoplasms were similar to those seen after conventional therapy.

Discussion

Conflicting results concerning the possible carcinogenicity of cyclosporine have been reported. In two studies, no cancers developed in dogs, sheep, pigs, rodents, and rabbits treated with cyclosporine only (8, 9). In addition, rabbits and rats treated with cyclosporine and steroids and followed for 1 to 2 years had no evidence of malignancy (8). Yet in vitro studies of human cells showed that cyclosporine induces sister chromatid exchanges and is, therefore, mutagenic (10). However, the concentrations of cyclosporine (1 μg/ml) used in the experiments were much higher than those used clinically. Lymphomas did develop in nonhuman primates treated with varying doses of cyclosporine, with or without other immunosuppressive agents, after transplantation of the heart or heart and lungs. These occurred in 12 of 97 animals at risk for two weeks or longer after transplantation (11). A herpeslike virus having antigens cross-reactive with Epstein-Barr virus was found in the cancer cells. As mentioned above, Epstein-Barr virus is suspected of causing lymphomas in human recipients of renal transplants (12).

TABLE 2

Comparison of Number of Common Tumors Following Cyclosporine and Conventional Immunosuppression

Tumor type or site	Conventional	Cyclosporine
	No. (%)	No. (%)
Skin	1,019 (40)	21 (16)
Lymphomas	318 (12)	56 (43)
Cervix	151 (6)	3 (2)
Kaposi's sarcoma	85 (3)	11 (8)
Vulva or perineum	74 (3)	0 (0)
Total no. of tumors	2,565*	131

* Occurred in 2,391 patients.

In another study lymphoproliferative lesions were produced in rats given dietary cyclosporine (13). The lesions closely resembled those described in humans in their affinity for gut-associated lymphoid tissues and their morphologic appearance. The authors suggested that cyclosporine, by inhibiting signals from T-cells in response to antigens, causes excessive B-cell responses leading to lymphoproliferative disorders. In other words, chronic cyclosporine administration interferes with immune regulatory mechanisms. The authors thought that the lesions might be reversible.

Total Dosages of Immunosuppressants. What is the explanation for the discrepancies in the animal experiments mentioned above and for the variable incidence of lymphomas and other tumors reported to the CTTR from transplant centers? Apart from the species differences, a major factor appears to be differences in the dosage of cyclosporine. In one study, lymphomas occurred after administration of large doses but not when the dosage was reduced (14). Another important variable is the use of other immunosuppressive agents. Only 5% of the patients in the present series received treatment with cyclosporine alone. In about 5,550 transplant patients treated with cyclosporine, the incidence of lymphomas and lymphoproliferative lesions was

0.4% in patients given cyclosporine alone or together with low-dose steroids but 8% in those given cyclosporine in combination with other immunosuppressive agents (2). The risks of overimmunosuppression, particularly when several drugs are used concomitantly, cannot be overemphasized (5, 15). The various cancers described above are complications of immunosuppression, not a side effect of any single agent, such as cyclosporine or azathioprine.

A gratifying feature of the cyclosporine-related lymphomas is that complete remissions have followed drastic reduction of immunosuppressive therapy, either alone or together with other measures such as surgery or radiotherapy (16). In one study, 11 of 16 transplant patients with lymphomas (most of whom had received cyclosporine and prednisone) were alive and free of their tumor after such treatment (16).

Carcinogenic Potential and Length of Follow-Up. At present, the average length of follow-up of cyclosporine-treated transplant patients is much less than that of their conventionally treated counterparts. With longer follow-up the types of cancer may change. Experience with conventional immunosuppressive therapy has shown that certain tumors appear at fairly well defined time periods after transplantation. Kaposi's sarcomas appear at an average of 24 months after transplantation, lymphomas at an average 42 months, other tumors at an average of 63 months, and carcinomas of the vulva and perineum at an average of 93 months. With longer follow-up of cyclosporine-treated patients we may duplicate the experience with conventional immunosuppression: the most common early neoplasms were lymphomas (3), but with longer follow-up other malignancies, mainly carcinomas of the skin and lips, in situ carcinomas of the cervix, and carcinomas of the vulva and perineum, were observed (4–6). Long-term follow-up of large numbers of patients treated exclusively with cyclosporine will clarify the carcinogenic potential of this agent in humans.

Some workers (17) have suggested that cyclosporine stimulates proliferation of squamous epithelium and skin appendages (manifested by skin thickening and hypertrichosis), which may develop into cancer in the abnormal skin of patients previously treated with azathioprine and prednisolone who are converted to cyclosporine therapy. However, only 13 squamous cell carcinomas and 8 basal cell carcinomas of the skin following cyclosporine therapy have been reported to the CTTR. It appears that skin cancer is not a major problem at present, but the picture may change as patients are followed up for longer periods.

Other Questions. One might speculate about the etiology of the 16 carcinomas of the breast, testis, cervix, ovary, vagina, prostate, and thyroid in this small series of 131 cancers. They may be merely chance events, but they do raise the question whether cyclosporine has hormonal side effects that causes tumors in these organs.

One might also speculate on the five renal carcinomas in this series. Were they coincidental, or could they be related to the nephrotoxicity of cyclosporine?

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Cyclosporine and Liver Transplantation

R. Y. Calne

Both liver transplantation and cyclosporine are now accepted parts of surgical therapy. In the early experience with liver transplantation, the importance of rejection after the transplantation was difficult to determine because of the sickness of the patients when they received transplants, the major intervention of the surgery, and the many postoperative complications that occurred. Thus only a few patients died of rejection, whereas a number succumbed to infection brought about by immunosuppressive treatment. In certain animals, particularly pigs and rats, liver grafts are able to withstand the immune attack of rejection, which can resolve spontaneously, leading to a state of operational tolerance; there is no evidence that a similar phenomenon occurs in humans. Now that patients are referred for liver transplantation earlier in the course of their fatal disease and surgery has become more routine, it is becoming clear that some degree of rejection is to be expected in the majority of patients, usually between the fifth and tenth postoperative days.

Selection of patients, assessment, the donor and recipient operative details, and preservation are outside the scope of this short article.

Diagnosis of Rejection. It can be very difficult to diagnose rejection on clinical grounds. If the patient is well and has steadily improving or normal liver function, significant rejection can be excluded. If there are any changes in liver function indicating cholestasis or liver cell damage, rejection is a possibility, although other causes of liver dysfunction—such as obstruction of biliary drainage, recurrence of hepatitis, development of cytomegalovirus infection, bacterial cholangitis, and adverse reaction to drugs—must be excluded. Both azathioprine and cyclosporine can be hepatotoxic. Poor liver function continuing from the time of operation may be due to damage to the donor liver before it was removed, as in organs recovered from donors who were alcohol or drug abusers or damage during the removal, preservation, and transplanting of a graft. It is our policy to do a needle biopsy of the liver early in the postoperative course if there is not a steady improvement of liver function. Interpretation of the biopsy by an experienced pathologist is usually helpful in giving a positive diagnosis of rejection, provided antirejection therapy has not been given. A particularly virulent form of rejection, which usually occurs more than a month after transplantation, involves progressive cholestasis with disappearance of small bile ducts within the liver—the so-called vanishing bile duct syndrome. So far, the only treatment that has been of any avail in this condition has been a retransplantation operation.

Immunosuppression. Since many patients referred for liver transplantation have impaired renal function due to their liver failure, it is not surprising that cyclosporine, which is a nephrotoxic drug, can cause the patient to develop complete renal failure with acute tubular necrosis, requiring dialysis for two to three weeks. This is especially likely if nephrotoxic antibiotics or other drugs that can damage the kidneys are given. Because of this danger, we start the patient on azathioprine and steroids in the same dosage used for kidney transplantation, namely 2 mg/kg per day for prednisolone and 1.5 mg per day for azathioprine. When renal function has

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Adapted from the seminar "Cyclosporine: 1986 and Beyond" presented at The Mount Sinai Medical Center, New York City, on April 5, 1986, sponsored by the Department of Surgery and The Page and William Black Post-Graduate School of Medicine of the Mount Sinai School of Medicine (CUNY) and directed by Lewis Burrows, M.D. The program was supported in part by an educational grant-in-aid by Sandoz, Inc. Pharmaceutical Division.

been shown to be satisfactory, cyclosporine is started cautiously with two intravenous infusions of 2 mg/kg, each lasting two hours, giving a total of 4 mg/kg per day. Cyclosporine is not given by mouth until the T-tube inserted into the biliary drainage system has been clamped and bile is present in the duodenum. To give cyclosporine orally before this will be unhelpful, since little will be absorbed.

In assessing the dosage of cyclosporine, care must be taken in interpreting blood levels determined by radioimmunoassay, since metabolites of cyclosporine will be measured together with the parent compound. Determination of blood levels by high-performance liquid chromatography (HPLC) is preferable. A patient progressing satisfactorily will, for a short period of time, receive azathioprine, steroids, and intravenous cyclosporine. The patient will be converted to oral cyclosporine when the T-tube is clamped, and then the steroids and azathioprine will be reduced slowly over the course of two to three months. The T-tube is usually removed at three months, and patients doing really well will be maintained only on cyclosporine. Patients with some slight impairment of liver function will in addition have small doses of maintenance steroids, perhaps 10 mg of prednisolone per day.

Treatment of Rejection. Treatment of rejection consists initially of three daily doses of 1 g of solumedrone given slowly intravenously. If, after 3 days, there is no improvement in the next 48 hours, a further 3 days' treatment is given. If there is still no improvement, we have used a monoclonal antilymphocyte antibody, Campath-1, or a combination of Campath-2 and Campath-3 for up to 10 days, which has sometimes led to recovery. If the patient is undergoing progressive impairment of liver function despite antirejection treatment, then the offer of a retransplantation is made. Retransplantation is performed as soon as possible, since the procedure becomes progressively more difficult as time passes and adhesions weld the liver in a mat of fibrous tissue.

Conclusions. After operation, patients with inborn errors of metabolism such as α_1-antitrypsin deficiency, Wilson's disease, or biliary atresia will not be in danger of recurrence of their original disorder in the transplant. However, most other diseases can recur, particularly malignancy, hepatitis, alcoholism, and probably primary biliary cirrhosis and chronic active hepatitis.

A prospective long-term study will be required to determine whether matching for HLA antigens and prior blood transfusion are important in the prognosis of liver transplants. In view of some recent reports on kidney transplantation, it may well be that when cyclosporine is used, the tissue typing and blood transfusion effects may not be relevant, but this remains to be seen in the long term. For the present, a one year survival rate of approximately 60%, or perhaps slightly higher for children, can be expected after liver transplantation. Patients doing well at one year, who are probably about half of those surviving at one year, can be expected to have good rehabilitation for a number of years; but liver transplantation has not been performed long enough for a definitive prognosis to be given to the patient, the longest survival to date having been seventeen years.

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Cyclosporine Experience in Renal Transplantation in Children

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Transplantation is considered the optimal therapeutic modality for children with end-stage renal disease (1). This bias is common to most pediatric nephrologists and is based on the belief that the quality of rehabilitation following a successful transplantation is far superior to that achieved with various forms of dialysis. Despite improved graft survival, however, suboptimal growth is frequent in children who have had a successful transplantation (2). The primary factor affecting this suboptimal growth is the dosage of corticosteroids required for immunosuppression. The added burden of cushingoid features due to steroid therapy frequently leads to noncompliance with the therapy with resulting graft loss, particularly in adolescents (3).

Cyclosporine, a peptide fungal derivative, appears to have a steroid-sparing effect. Rejection in a nonimmunosuppressed patient is triggered by an antigen that stimulates macrophages to release interleukin-1. Release of interleukin-1 induces interleukin-2 production from helper T cells. Under interleukin-2 stimulation, sensitized lymphocytes proliferate, leading to the rejection phenomenon. Corticosteroids act to block interleukin-1 production. Although the primary action of cyclosporine appears to be blockage of interleukin-2 production, cyclosporine also blocks interleukin-1 (4, 5).

Cyclosporine has been used at our institution since 1983 for renal transplantation. The specific aim is to utilize its steroid-sparing effect and to maintain the renal graft with cyclosporine as the sole immunosuppressant. In order to put the efficacy and the toxicity of the drug in children in a proper perspective, this study is limited to children who received the drug for at least 6 months or who died before the end of the 6-month period. Data are compiled up to December 1985.

Materials and Methods

Two groups of children were treated with cyclosporine. Group A consisted of 23 children who started with cyclosporine at the time of transplantation. Group B consisted of 14 children who had received a transplant earlier, were on conventional therapy (azathioprine and prednisone), and were converted from azathioprine to cyclosporine.

The dose of cyclosporine to patients in group A was 3 mg/kg intravenously for the first 2 days, followed by an oral dose of 10 mg/kg beginning on day 3. The cyclosporine dose was gradually reduced after the first week to achieve a maintenance dose of 6 mg/kg by the 12th week. The posttransplant cyclosporine dose was adjusted by weekly whole-blood trough-level measurements, using a high-performance liquid chromatography (HPLC) technique. The effective blood level aimed at was between 100 and 200 ng/ml.

The prednisone dose to patients in group A was 0.5 mg/kg on the day of transplantation. This was gradually reduced to 0.1–0.2 mg/kg by 12

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Adapted from the seminar "Cyclosporine: 1986 and Beyond" held at The Mount Sinai Medical Center, New York City, on April 5, 1986, sponsored by the Department of Surgery and The Page and William Black Post-Graduate School of Medicine of the Mount Sinai School of Medicine (CUNY) and directed by Lewis Burrows, M.D. The program was supported in part by an educational grant-in-aid by Sandoz, Inc. Pharmaceutical Division.

TABLE 1
Group A (23 Patients) by Transplant Status

Transplant status	No. of patients
Cadaveric	11
Live related donor	12
First transplant	14
Second transplant	9

TABLE 2
Reasons for Conversion to Cyclosporine Therapy in Group B (14 Patients)

Reason	No. of patients
Unstable graft	4
Possible growth	5
Steroid toxicity (obesity, acne)	3
Poor compliance on prednisone	2

TABLE 3
Side Effects of Cyclosporine Therapy in 37 Patients

Side effect	No. of patients
Gingival hyperplasia	11
Hypertrichosis	9
Seizures	2
Anemia	2

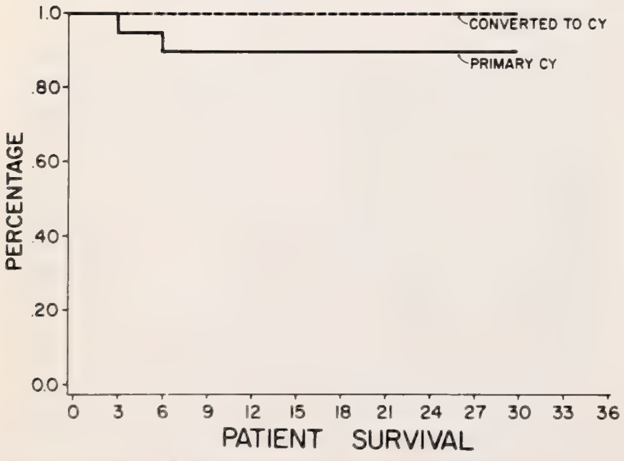
weeks. If the function of the renal graft remained stable, attempts were made to discontinue prednisone over the next 4 to 8 weeks.

Patients in group B received 6 mg/kg cyclosporine orally on the first day of conversion to cyclosporine, together with half of their previous dose of azathioprine. On the second day of conversion azathioprine was discontinued. The cyclosporine dose was adjusted after the first week to obtain an effective blood level of 100–200 ng/ml as determined by HPLC.

The prednisone dose in group B patients was maintained for the first 4 weeks at the same level they had received before conversion. If graft function remained stable, attempts were made to discontinue prednisone over the next 4 to 8 weeks.

Since no previous experience or information was available regarding the conversion from azathioprine to cyclosporine in children, initially patients in group B were admitted to the hospital for 3 days to carry out the conversion. As experience was gained, subsequent conversions were carried out in an outpatient setting. As outpatients, children in both groups were monitored once or twice a week, as needed, for evidence of renal dysfunction and cyclosporine hepatotoxicity. Acute rejection episodes in both groups were diagnosed using the following criteria: (a) rise in serum creatinine to a level greater than 0.3 mg/dl, (b) evidence of sulfur colloid uptake on a radionuclide scan (6), and (c) histologic evidence of a diffuse lymphocytic infiltrate on transplant biopsy. Therapy for rejection consisted of methylprednisone given in doses of 50–200 mg/day, depending on the weight of the patient, for 5 to 7 days. When rejection was not reversed by methylprednisone therapy, antithymocyte globulin was used for 10 to 14 days. To reverse rejections that did not respond to other therapy, OKT_3 monoclonal antibody was used.

Endogenous Cortisol Measurements. In patients from both groups who were able to stop taking prednisone, NaCl tablets were prescribed at 500 to 1000 mg/day from the day of discontinuation for 2 weeks. At the end of 2 weeks an ACTH stimulation test was done. A synthetic ACTH (Cor-



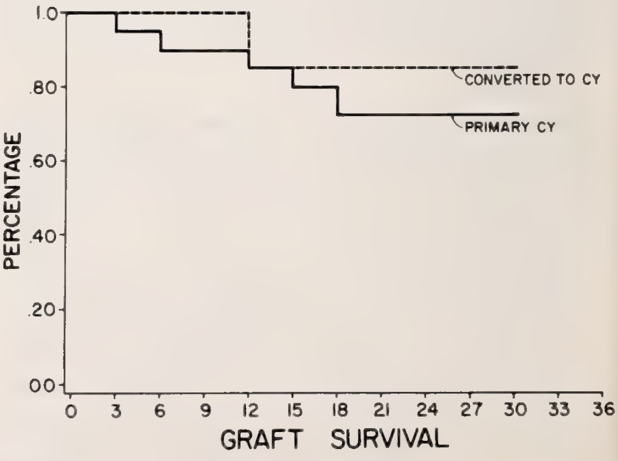


Fig. 1. Left Actuarial patient survival in months; CY, cyclosporine. **Fig. 2. Right** Actuarial graft survival in months.

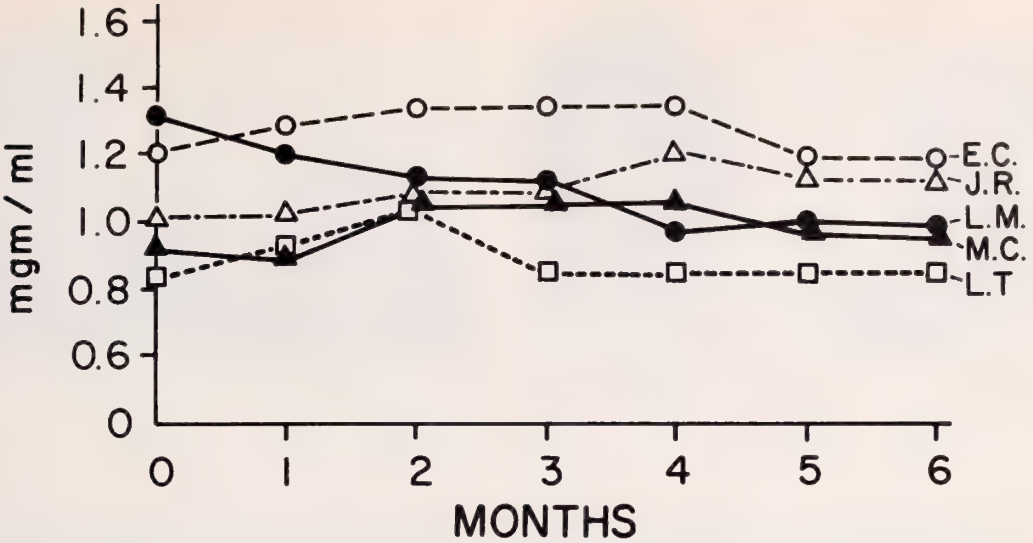


Fig. 3. Serial serum creatinine values of five patients during first 6 months after discontinuation of prednisone.

trosyn) was administered intramuscularly at a dose of 0.125 mg for children under 2 years of age and 0.250 mg for children older than 2 years. Blood was drawn for serum cortisol measurement prior to ACTH stimulation and 1 hour later. If the stimulation test showed adequate endogenous cortisol production, administration of NaCl tablets was discontinued.

Growth Hormone Levels. In prepubertal children who were able to discontinue prednisone, growth hormone levels were measured after methyldopa stimulation. Patients were kept fasting overnight, and 500 mg of methyldopa was administered orally the next day. Blood samples were taken for growth hormone measurements at 0, 20, 40, 60, 90, and 120 minutes after administration of methyldopa. In some patients growth hormone measurements were carried out on two separate occasions—while the patients were still receiving prednisone and 1 week after discontinuation of prednisone—in order to determine the influence of prednisone on growth hormone levels.

The effect of treatment on survival of patients and survival of grafts was analyzed with product limit estimators of survival curves (7). Patient survival and graft survival were calculated separately for both groups. In the analyses the day of conversion in patients of group B was considered the first day.

Results

Table 1 shows characteristics of patients in group A, and Table 2 shows the factors necessitating conversion to cyclosporine in group B patients.

Patient Survival. None of the patients converted to cyclosporine from conventional therapy died, and actuarial patient survival at 30 months was 100% (Fig. 1). Two of the patients in group A died, resulting in a 30-month actuarial patient survival of 94%. Both of the patients who died were recipients of a second transplant. The first was an 8-year-old male with focal segmental sclerosis as the primary disease. He received a kidney donated by his father. Five months after transplantation and a month after steroid therapy was discontinued, his serum creatinine level was 0.6 mg/dl and he was receiving 6 mg/kg cyclosporine per day. He developed pyrexia 5 months after transplantation and after a delay of 2 days he was hospitalized. Eighteen hours after hospitalization he died of *Staphylococcus epidermidis* septicemia. The second patient was a 16-year-old female recipient of a second cadaveric graft. The graft functioned poorly and she had an

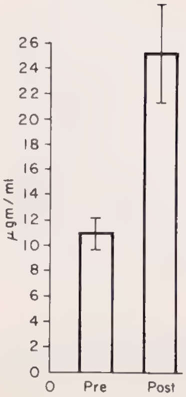
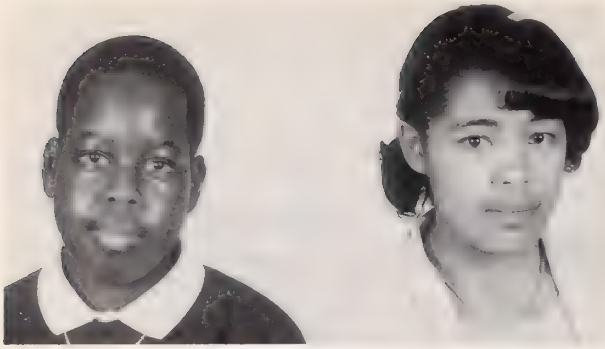


Fig. 4. Mean serum cortisol concentrations before and after ACTH stimulation in patients able to discontinue prednisone.



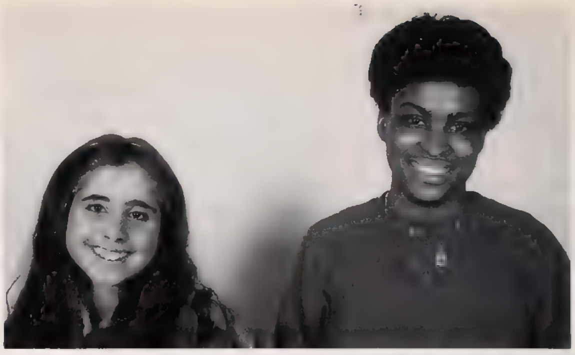


Fig. 5. Left Patient on left receives 5 mg of prednisone daily. Patient on right has not received prednisone for nine months.
Fig. 6. Right Two patients, both recipients of a cadaveric kidney, who have not taken prednisone for more than 2 years and have not had an episode of rejection. Serum creatinine level of each patient is 1.3 mg/dl.

acute rejection episode in the first month. The patient was treated with methylprednisone for reversal of the rejection, but she developed herpes viremia and died suddenly.

The 30-month actuarial graft survival was 72% for group A (primary cyclosporine) and 84% for group B (converted to cyclosporine) (Fig. 2). Graft losses in group A were all in recipients of a second transplant, whereas of the two grafts lost in group B, one was due to noncompliance and the other was due to chronic rejection of an unstable graft.

Rejection Episodes. We compared the number of rejection episodes in patients in group B over an 18-month period prior to and following conversion to cyclosporine therapy. Both the mean number of rejection episodes and the mean number of days spent in hospital were significantly reduced after conversion. The mean number of rejection episodes per patient was 3.5 (range 1–10) before conversion and 1 (range 0–4) after conversion. The mean number of days in hospital was reduced from 39 (range 2–82) to 10 (range 0–42), a statistically significant difference ($p < .05$) by Student's *t* test.

Side Effects of Cyclosporine Therapy. The major side effect of cyclosporine has always been nephrotoxicity. We considered a rise in serum creatinine of more than 25% over the baseline value with a negative sulfur colloid scan and the absence of lymphocytic infiltration on transplant biopsy to be indicative of nephrotoxicity, particularly when associated with a high blood level of cyclosporine. Several patients required lowering of the cyclosporine dose, but for the duration of this study no patient showed irreversible nephrotoxicity or required complete withdrawal of cyclosporine.

Of the other side effects of cyclosporine therapy (Table 3), gingival hyperplasia occurs more frequently in children with poor dental hygiene. Hypertrichosis in which the excessive hair growth has a normal distribution occurs more frequently in children with a darker complexion—a concern in adolescent girls. Seizures, though only a small percentage of patients are subject to them, are a major concern, since anticonvulsant therapy leads to difficulty in maintaining adequate cyclosporine levels.

Discontinuation of Prednisone. A total of 21 children were able to discontinue prednisone, but the drug had to be reinstituted in 7 children when a rejection episode occurred within 1 to 3 months. The remaining 14 patients were able to discontinue prednisone for 4 to 27 months. Of these 14 children, 11 are in group A and 3 in group B. The mean serum creatinine level in these 14 patients is 1.1 mg/dl (range, 0.6 to 1.8 mg/dl). Although the serial serum creatinine values of some of the patients show a transient rise over a 6-month period after discontinuation of prednisone (Fig. 3), the value at 6 months after discontinuation is unaltered from the baseline value.

Endogenous Cortisol Production. Figure 4 shows the serum cortisol levels (mean ± standard deviation) before and after ACTH stimulation for all patients who were able to discontinue prednisone. A twofold rise in serum cortisol following ACTH stimulation shows that the pituitary-adrenal axis is intact. Individual values (not shown) indicated that all patients had adequate endogenous cortisol reserves.

Growth and Psychological Well-being. The contrast between the physical features of children receiving low-dose (5 mg/day) prednisone and those receiving no prednisone therapy is marked (Fig. 5), as is the total rehabilitation of patients receiving cyclosporine alone (Fig. 6).

Growth hormone levels after methyldopa

stimulation in five of the prepubertal children (Fig. 7) were examined after discontinuation of prednisone therapy. A stimulated growth hormone level greater than 10 ng/ml observed at any time during the 2-hour test period is considered normal. Using this definition, four of the five children showed adequate growth hormone levels. The peak level of growth hormone response of another prepubertal child was 9 ng/ml during steroid therapy and 19 ng/ml after discontinuation of the therapy (Fig. 8).

Catch-up growth in boys (Fig. 9) and girls (Fig. 10) following discontinuation of prednisone was plotted, as was the remarkable growth spurt in two infant boys being maintained on cyclosporine as the sole immunosuppressant (Fig. 11).

Need for Prednisone during Stress? One of the patients in group A was a 17-year-old girl who became pregnant 1 month after discontinuing prednisone. She was the recipient of a second cadaveric transplant and had a serum creatinine level of 1 mg/dl at the time of conception. With the increase in renal blood flow due to the hemodynamics of early pregnancy, her serum creatinine level decreased at first (Fig. 12) but stabilized over the next few months. She did not require any additional prednisone throughout her pregnancy.

Discussion

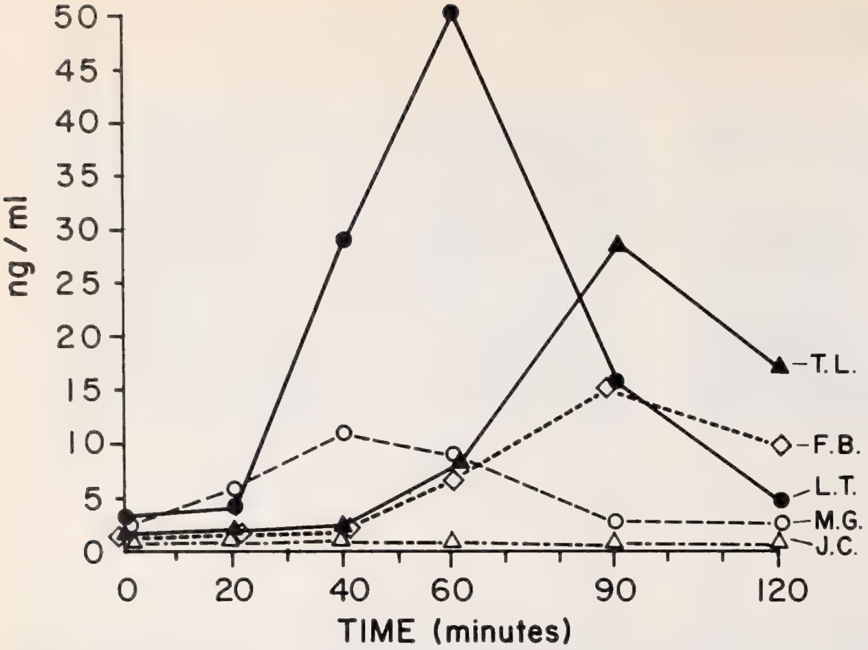
The multiple side effects of maintenance corticosteroid therapy makes finding a safer and more effective chemical immunosuppressant highly desirable. The striking similarities between the modes of action of steroids and cyclosporine at the cellular level (8) has enabled transplant immunologists to utilize the steroid-sparing action of cyclosporine and thus reduce the side effects of steroid therapy.

Cushingoid Features. Transplant patients receiving steroid therapy do not inevitably develop cushingoid features, which vary from patient to patient. The cushingoid signs are more frequent in females and are probably related to decreased total body clearance of prednisolone (9). Noncompliance with steroid therapy because of this disfigurement is common in young adolescents and jeopardizes graft survival (3). There seems to be a consensus among transplant clinicians that low-dose or alternate-day therapy with steroids does not affect the facial features of a child. As shown in Fig. 5, this is not an accurate observation, and only total discontinuation of prednisone can restore the physiognomy to normal. The disappearance of cushingoid facies in our study patients (Figs. 5, 6) appears to have had a salutary effect on the overall well-being and self-esteem of the children, particularly the adolescent girls, and has reduced the problem of noncompliance.

Damage to Growth. In contrast to the individual variability of cushingoid effects, the growth-damage effects of steroids are universal in children. Many theories have been put forward to explain the mode of action of steroids in inhibiting growth (10), but the specific sites at which steroids interfere with growth remain unknown (11). Our observation that some of the prepubertal children in this study had higher growth hormone levels after discontinuation of steroid therapy is interesting but needs confirmation. Phillips and co-workers (12, 13) have partially characterized a somatomedin inhibitor in the serum of uremic patients. This low-molecular-weight substance appears to be present in normal urine and may not be filtered by the uremic kidney. These workers have also demonstrated that the bioactivity of circulating somatomedin falls 6 hours after steroid administration in children receiving steroid therapy for renal transplantation. This suggests that concentrations of normally present somatomedin inhibitors increase after steroid administration (14).

Since the majority of the prepubertal children in our study showed adequate growth hormone levels, growth potential obviously exists, and the removal of steroid inhibition should result in a growth spurt. In this regard our preliminary data (Figs. 9–11) are encouraging. Other pediatric renal transplant centers that use cyclosporine with prednisone are now reporting improved stature in cyclosporine-treated patients (15–18). Cyclosporine does not have any growth-stimulating action, hence the improvement noted must be due to the lower maintenance dose of prednisone employed in conjunction with cyclosporine.

The significant improvement in graft survival with cyclosporine therapy noted in the initial American (19, 20) and Canadian studies (21) has been confirmed in long-term follow-ups (22, 23). However, only scattered reports of the use of cyclosporine in children have been presented (24–27), and in these studies cyclosporine was used in conjunction with prednisone. Whether maintenance prednisone is necessary for renal graft survival is questionable. In a European multicenter study (28), 82% of the patients in the cyclosporine group did not receive maintenance prednisone and 27% of the patients never received any steroids. Long-term evaluation by a



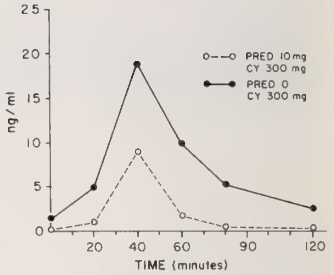
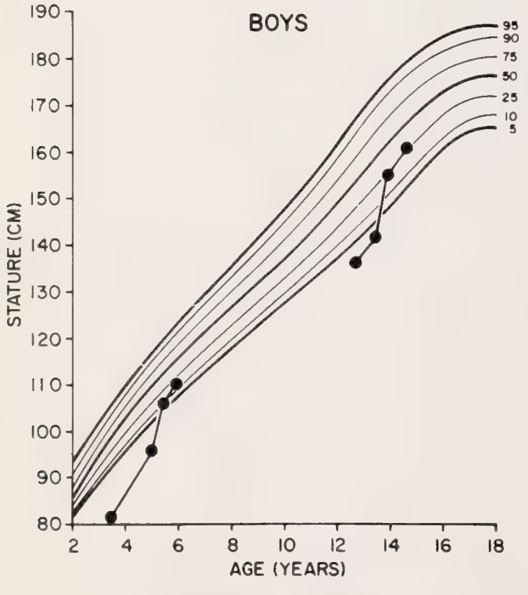
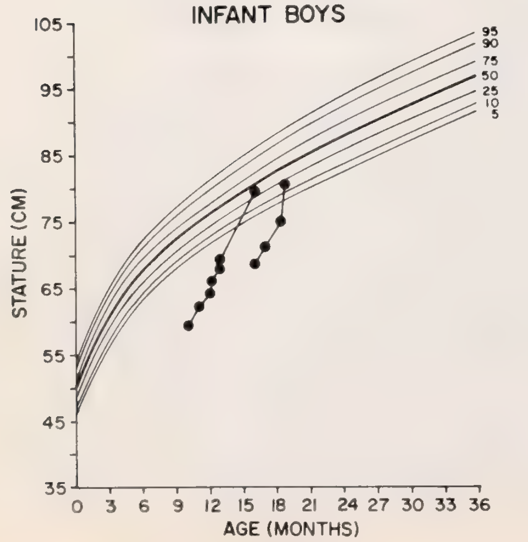


Fig. 7. Left Growth hormone levels of five prepubertal children following stimulation with methyldopa. **Fig. 8. Right** Growth hormone levels in a prepubertal child during and after prednisone therapy; PRED, prednisone; CY, cyclosporine.





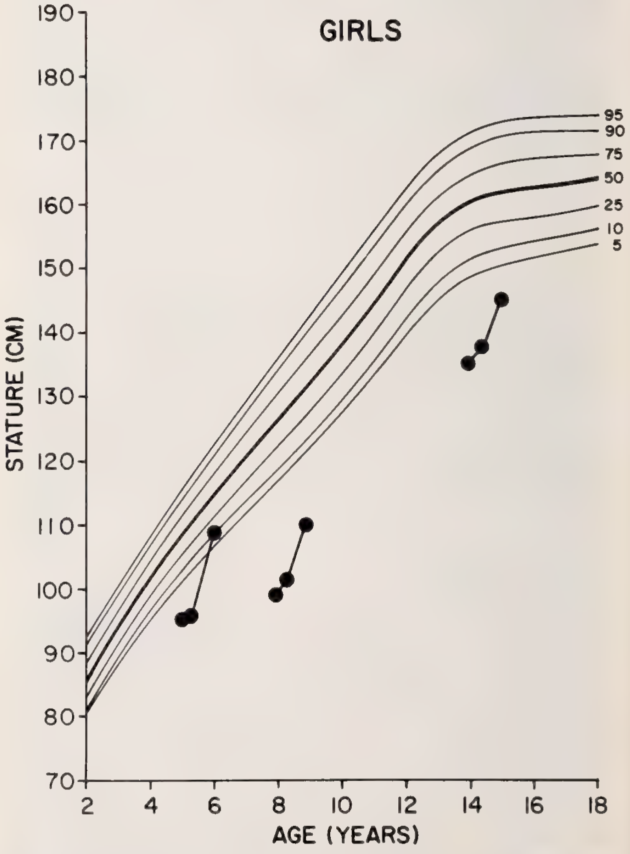


Fig. 9. Above left Catch-up growth of two prepubertal boys after discontinuation of prednisone at second measurement, plotted against 5th to 95th percentiles of boys' stature by age in years. **Fig. 10. Above right** Improved velocity of growth of three prepubertal girls after discontinuation of prednisone at second measurement, plotted against 5th to 95th percentiles of girls' stature by age in years. **Fig. 11. Left** Rapid growth of two male infants after discontinuation of prednisone at second measurement, plotted against 5th to 95th percentiles of infant boys' stature by age in months.

Cambridge, England, team (23) shows that cyclosporine therapy without steroids is capable of sustaining a high percentage of cadaveric renal grafts over a period of 4 years. Neither the European multicenter study nor the English study, both of adults, nor our initial data on children (29) were controlled, but randomized data from the Canadian study (30) have shown one-year graft survival in 84% of the patients receiving cyclosporine with steroids, compared to 88% of the patients receiving cyclosporine alone.

Our current data support previous observations of adult graft recipients that serum creatinine levels are higher in patients treated with cyclosporine than in those receiving conventional therapy (31, 32). However, there does not appear to be any further rise in serum creatinine levels after discontinuation of prednisone, as shown in Fig. 3. It is too early to determine whether the slightly higher serum creatinine levels in children treated with cyclosporine portend progressive renal functional deterioration; however, we have not noted any further rise in serum creatinine levels of children who have stable graft function for 24 months after transplantation. Furthermore, the most recent data from the Canadian study show stable serum creatinine levels in a follow-up at 36 months (22).

Despite the host of techniques used by us and others (6, 33–35), it is difficult to differentiate nephrotoxicity from rejection. A controlled trial of high-dose versus low-dose cyclosporine therapy (36) in our adult transplant recipients indicates that the incidence of nephrotoxicity is dose-related. Episodes of renal dysfunction were noted in 66% of 64 high-dose recipients, compared to 14% of 58 low-dose recipients, a statistically significant difference by chi square test ($p < .01$). Our protocol, using some of the lowest cyclosporine doses ever described in children, is thus designed to minimize nephrotoxicity. A fall in the level of serum creatinine with a reduction in the dose of cyclosporine, particularly when accompanied by an appropriate blood level of cyclosporine, appears to be the best retrospective evidence of nephrotoxicity.

Apart from nephrotoxicity, the only major side effect in children that merits mention is convulsions. Two of the children under 6 years of age in our study sustained seizures while being treated with pulses of methylprednisone during a rejection episode and needed anticonvulsant therapy. Both phenobarbital and dilantin are inducers of the cytrochrome P-450 enzyme system in the liver and cause rapid elimination of cyclosporine from the body. This results in inability to maintain an adequate cyclosporine level for graft tolerance. Use of higher doses of cyclosporine (8–10 mg/kg) divided into two or three oral doses is necessary in the presence of anticonvulsant therapy.

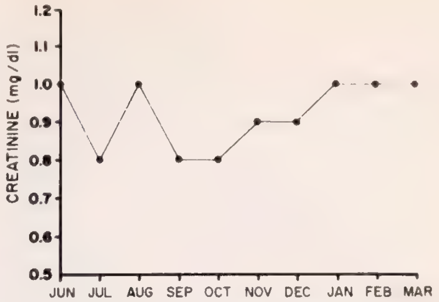


Fig. 12. Serum creatinine levels during 9 months of an adolescent girl's pregnancy; she was receiving 5 mg/kg cyclosporine daily.

In animals, cyclosporine has been shown to be without any teratogenic effect when doses are in the well-tolerated range (up to 17 mg/kg per day in rats and up to 30 mg/kg per day in rabbits (37). About a half-dozen successful pregnancies without teratogenicity have been recorded in women receiving cyclosporine (38), but most of the babies were small for their gestational age (39, 40). The successful pregnancy of one of the adolescent girls in this study, whose baby was normal for its gestational age, suggests that addition of steroids may play a role in producing a baby who is small for gestational age. Careful monitoring of the cyclosporine level and of the pregnancy appear to be the only additional precautions necessary for patients with good graft function.

In summary, our study shows that:

- children tolerate cyclosporine well with few side effects;
- cyclosporine can be used as the sole maintenance immunosuppressant in selected recipients of organs from live related donors and cadavers;
- cyclosporine can be used as the sole maintenance immunosuppressant in selected patients who start with it at the time of transplantation as well as patients who are converted from conventional therapy later on, provided they have stable graft function;
- all children who have had their prednisone withdrawn exhibit adequate endogenous cortisol reserves;
- the majority of prepubertal children who have discontinued prednisone have sufficient growth hormone reserves to provide a potential for growth.

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Small-Bowel Transplantation: An Overview

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The technical feasibility of intestinal grafting and the reacquisition of function produced by small bowel autografts was shown nearly three decades ago in dogs by Lillihei and his associates at the University of Minnesota (1). This and succeeding reports (2–4) set forth the concept that transplantation of the small bowel could become a potentially curative treatment for patients suffering from short bowel syndromes secondary to massive intestinal resections. On the basis of the early success of kidney transplantation in humans, potentially successful small bowel transplantation seemed an attractive and rational approach to the management of a large number of patients undergoing extensive intestinal resections for vascular accidents or for diffuse intestinal diseases such as Crohn's disease.

Interest in the field, however, remained limited for several reasons. The first was that improvement in total parenteral nutrition was life saving and allowed the survival of patients for extended periods of time. The second, and perhaps more important, factor was the early demonstration that immunosuppressive therapy based on steroids, antimetabolites (such as azathioprine), and antilymphocytic sera was quite ineffective at preventing rejection of small bowel allografts (5–9). The failure due to technical and immunologic problems of seven attempts at small bowel grafting in humans between 1964 and 1970 (10) further contributed to the decline of interest in the field.

The discovery of cyclosporine (11) and the demonstration of its exceptional immunosuppressive properties in clinical transplantation of the heart, heart and lung, liver, kidney, and bone marrow (12) has restimulated considerable interest in small bowel transplantation. In the past few years a number of laboratories, including our own, have been engaged in experimental studies of small bowel (SB) transplantation in which cyclosporine was the main immunosuppressive agent (10, 13). It is the purpose of this review to describe some of the experiences of the past as well as some recent developments in the field of SB transplantation.

Immunologic Aspects

The large amount of lymphoid tissue intimately associated with the gastrointestinal tract presents immunologic issues which set SB transplantation apart from other types of solid organ homografts. The unavoidable transfer to the host of donor lymphoid tissue along with the graft has two opposite and equally undesirable consequences for the transplanter.

The first undesirable consequence stems from the fact that lymphoid tissue can provide an exceedingly powerful immunogenic stimulus to the host (14), thereby increasing the need for and the complexity of immunosuppressive therapy. Lymphoid and lymphoreticular cells, such as dendritic cells (15), are richly endowed with both class I and II MHC alloantigens and are a sessile population. They can migrate rapidly out of the graft (16, 17) to central lymphoid organs, such as the spleen, or to lymph nodes, where they can set in motion a rejection and compound its intensity (18). Passenger leukocytes, broadly defined as nonparenchymal blood-borne cells present in organ graft, have long been thought responsible for providing the initial sensitizing stimulus resulting in the rejection of the organ (14, 19, 20). Lymphoreticular cells such as the dendritic cells have been shown to have a primary stimulatory role, particularly in the rat (21), although other

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cellular elements such as erythrocytes, lymphoid cells, and vascular endothelial cells can contribute to the antigenicity of the graft (18). In this context, it becomes apparent that a richly vascularized organ graft, such as an SB allograft, containing large amounts of lymphoid tissue in the form of Peyer's patches and mesenteric lymph nodes, presents an unusually strong and complex alloantigenic challenge to the recipient.

The second negative aspect of the presence of lymphoid tissue in the graft stems from the ability of the donor's alloreactive T cells to migrate out of the graft and generate a graft-versus-host reaction (GVHD) akin to the graft-versus-host disease observed in recipients of allogeneic bone marrow. The potential of SB allografts to generate lethal GVHD was most clearly demonstrated in inbred rats by Monchick and Russell (8) using a parental (LEW) SB graft to F1 (LEW × BN) hybrid recipients. Under these conditions, GVHD can be fully expressed, since the F1 hybrids, by virtue of the fact that they carry the parental haplotype, cannot reject the graft. Other investigators have more recently confirmed these observations in similar models and have documented the natural history of the disease, which involves lesions of the skin, liver, lymphoid organs, and native bowel of the recipient (22–24).

Although GVHD has also been described in dogs receiving allografts of the entire small bowel (2, 25), other investigators have not made the same observation in domestic pigs (13, 26). Rejection, rather than GVHD, also appears to be the predominant reaction in rat models employing fully allogeneic donor-recipient pairs (13). Taken together, these observations suggest that GVHD may be of less significance than predicted by the results of experiment employing parental-to-F1 SB grafts. These models, in fact, tend to overemphasize the impact of GVHD since, in a fully allogeneic combination, the host would be capable of reacting against the graft and, under most circumstances, the host would be receiving immunosuppressive therapy which would also interfere with the expression of GVHD (27).

Although the impact of GVHD in human SB transplantation is difficult to predict, the threat of GVHD depends on factors such as the size of the graft and whether lymph nodes are transplanted along with the graft (22, 24), the degree of donor-recipient histoincompatibility, the immune status of the recipient, and the type of immunosuppressive therapy employed. These factors will obviously influence the host-versus-graft reaction, which on balance remains the major obstacle to SB transplantation.

Cyclosporine. Originally described by Borel as an antilymphocytic agent (11), cyclosporine (Cs) was shown to be a powerful immunosuppressive agent in experimental transplantation by Calne and his associates (28, 29). The successful clinical trials by Calne and coworkers that followed these and other experimental studies (30) opened the cyclosporine era in clinical transplantation (32). Innumerable studies in both experimental and clinical settings (33) have now established Cs as the mainstay of clinical immunosuppression in the transplantation of the heart, heart and lung, liver, kidney, pancreas, and bone marrow (12, 33).

Unlike conventional immunosuppressive agents, Cs has been shown to have a selective action on T cells by virtue of its ability to interfere with the action and production of lymphokines during the process of T cell activation (34). Remarkably, this action seems to be preferentially expressed on the T helper cell subset (34). The major disadvantage of Cs derives from its dose-dependent nephrotoxicity, which has generated considerable clinical problems and requires that the blood level of the drug be carefully monitored in transplant patients (34). Other side effects of the drug, such as hepatotoxicity, are quite mild.

Transplantation in Dogs. In view of the superior efficacy of Cs in preventing rejection of many organ grafts as well as GVHD (35), it is not surprising that several groups of investigators have begun to reconsider SB homografting as a possible treatment of short bowel syndromes. Some of the first studies employing Cs in SB transplantation were reported by Reznick et al (36) and were expanded in a subsequent report (37). These authors transplanted the entire SB in continuity in mongrel dogs. The superior mesenteric artery and veins were anastomosed to the aorta and inferior vena cava respectively. Cs treatment consisted of 25 mg/kg per day intramuscularly for thirty days and orally thereafter. The mean survival was slightly over 100 days, only three dogs surviving more than 200 days. The three long-term survivors eventually succumbed to rejection; the rest of the recipients died of other causes, prominently pneumonia.

Another group of investigators (38) transplanted orthotopically the entire SB in dogs. They obtained survivals ranging from one to four months in 10 and over 18 months in two recipients with an immunosuppressive regimen consisting of Cs (17 mg/kg per day orally) supplemented by prednisone. Five dogs died as a consequence of rejection and the other animals died of infections.

Aeder et al (39), using a model similar to the one described by Reznick et al (36), observed only a modest increase of graft survival in dogs treated with high Cs doses (20–40 mg/kg per day orally). The addition of azathioprine and antilymphocytic globulin did not improve the results significantly. Using an ectopic model in which a SB allograft was placed in the neck of dogs in a subcutaneous pouch with cutaneous enterostomies, Raju et al (40) reported graft survival of 56 days with Cs administered at 17 mg/kg per day orally. The addition of prednisone did not increase survival significantly.

Transplantation in Pigs. Two groups of investigators have recently reported studies of SB transplantation in the domestic pig. The results of these studies are similar to the ones obtained in dog models. Thus, Ricour et al (26) studied several Cs treatment protocols employing (600 cm) orthotopic and (200 cm) heterotopic grafts in piglets. Treatment of ectopic graft recipients with Cs at 25 mg/kg intramuscularly every other day resulted in rejection of all the grafts by day 20. But daily administration of oral Cs at the same dose resulted in no rejection of 9 of 13 grafts. Continuity between the graft and native bowel was reestablished in four of the surviving grafts, and Cs was continued at 12 mg/kg per day. The recipients were then sequentially sacrificed between day 80 and 390 without any sign of rejection. In the group of animals in which a larger graft was placed initially in the orthotopic position, oral Cs was not effective; 6 of 7 grafts were rejected. When oral Cs treatment was preceeded by 5 to 10 days of intravenous Cs treatment, however, the three recipients achieved long-term survival.

Pritchard and Kirkman (13), using heterotopic and orthotopic grafts in pigs and oral Cs at 25 mg/kg per day, did not succeeed in prolonging survival significantly. When the same dose of Cs was administered intramuscularly, prolongation of survival was observed in recipients of orthotopic grafts.

Transplantation in Rats. Cs was considerably more effective in rats. Indefinite survival of heterotopic LBN-to-LEW and prolongation of LWF-to-LEW allografts was reported with a 7-day course of Cs at 15 mg/kg per day (13, 27). Lee and Schraut (41) reported that a 7-day course of Cs, administered intramuscularly at 15 mg/kg per day, was effective in prolonging LBN and BN orthotopic grafts in LEW recipients. A more extended Cs course led to permanent survival of BN grafts. Hatcher et al (42), using a model in which F1 grafts (LEW × ACI) were transplanted heterotopically to parental strain rats (LEW), recently reported that oral Cs at 15 mg/kg per day prevented all histologic and functional changes associated with rejection.

Host Preconditioning with Cyclosporine and Donor-Specific Transfusions. From this review it is clear that while a measure of success was achieved in small animal models treated with Cs, the experience in large animals was less encouraging. Overall, the above studies indicate the need for very aggressive immunosuppressive therapy with high doses of Cs, a requirement not diminished by the concomitant administration of other immunosuppressive agents (e.g. 39, 40). In view of the well-documented dose-dependent nephrotoxicity of Cs in humans (34), it is difficult to envision a simple adaptation of these protocols to human SB transplantation. In view of these considerations, we have recently investigated (unpublished manuscripts) immunomanipulation of the host with blood transfusions and Cs as a way to increase the apparent limited efficacy of Cs in SB allograft recipients. The rationale for this approach was provided by a recent study from our laboratory in which we demonstrated (manuscripts submitted for publication) that long-term survival of heterotopic heart allografts could be achieved with subtherapeutic doses of Cs in rats conditioned with donor-specific transfusions and Cs (43). In an initial study (Martinelli GP et al. Small bowel transplantation in the rat: I. Effect of pretransplant transfusions and Cs on host survival.), using an orthotopic segmental SB allograft model (ACI to LEW), we demonstrated that host preconditioning with Cs and donor-specific transfusions was effective at reducing the need for high Cs doses. Thus, hosts treated with only 2.5 mg/kg per day of Cs survived a mean of two months, while control rats (conditioned with Cs and a third-party transfusion) succumbed to acute rejection in less than three weeks.

We then extended our study (Knight RK et al. Small bowel transplantation in the rat: II. Functional assessment of small bowel allografts in rats conditioned with transfusions and Cs.) to demonstrate that this form of conditioning was effective in prolonging survival of recipients entirely deprived of their native bowel and treated also with low doses of Cs. The results of our studies suggest that immunomanipulation of the host could be a possible solution to the apparent problem of low efficacy of Cs in SB transplantation. Should these studies be verified in larger animals, these protocols might be applicable to clinical SB transplantation, since recipient preconditioning with donor-specific transfusions and immunosuppressive agents has been an accepted practice at several transplant centers (44).

Techniques for Small Bowel Transplantation

The basic technique for orthotopic SB transplantation in dogs was described in 1959 by Lillihei and coworkers (1, 2). Revascularization of the graft was accomplished by anastomosing the superior mesenteric artery and vein to the same vessels in the recipient. The graft was then anastomosed in continuity with the native bowel. Technical failure rates, defined as graft failure within the first five postoperative days, were reported to be approximately 40%. Dogs receiving autografts suffered from diarrhea and weight loss for the first three weeks, then recovered and survived quite well in good general health. Regeneration of lymphatics was shown to occur within four to five weeks.

Reported variations on the technique in large animals consist mainly of differences in the site of venous anastomosis of the graft. Some investigators have chosen the vena cava (10, 36) as the site of venous drainage, others have selected the portal circulation (38). Establishing venous outflow in the systemic circulation is generally felt to be technically less demanding and, as suggested by Kirkman (10), would facilitate explantation of the graft in case of surgical complications or irreversible rejection. Advocates of the portal circulation as the more physiologic site of drainage point to the metabolic disturbances which result from establishing venous flow into the vena cava (45, 46). Although such disturbances are much less pronounced than the one observed with portacaval shunts, these investigators suggest that the use of hepatotoxic immunosuppressive drugs in patients with compromised liver function may result in more serious metabolic alterations of clinical significance. Another factor quoted in favor of portal drainage is its immunologic advantage. Thus, Sakai (47) reported prolongation of the rat kidney and Schraut et al (48) reported prolongation of SB allografts with portal venous drainage of the grafts. These advantages were not, however, observed in larger animal models (13).

The rate of technical failures reported in large animal models is quite high, ranging from 25% to 50% (13), vascular thromboses being by far the most common cause of graft failure. Low blood flow due to graft edema has been advanced as a possible cause of these problems (10). Further studies on SB preparation and preservation techniques are obviously needed. The rate of technical failures in orthotopic SB transplantation in small animal models has been in the 20% to 30% range (8, 41); in our experience it has been as low as 15% (49).

A number of heterotopic SB transplantation models have also been described for both small and large animals (4, 5, 9, 42). These are useful investigationally, although orthotopic models, or models in which the SB is transplanted in continuity with the native bowel, have greater clinical pertinence.

Functional Monitoring of Small Bowel Grafts

The development of functional tests that allow early detection of rejection episodes has been integral to investigations of SB transplantation. Although serial mucosal biopsies have proven to be an accurate way to monitor rejection (13), such procedures have the disadvantage of being invasive, and in a clinical setting would be hampered by the relative inaccessibility of the graft. Specimen processing time and the possibility of sampling error are further drawbacks of this monitoring system.

A number of absorption assays have been described as effective predictors of rejection episodes. Such assays involve the use of d-xylose (50), glucose (51), polyethylene glycol (42), and disaccharides such as maltose (52). Absorption of mono- or di-saccharides is impaired during a rejection reaction; the absorption of polyethylene glycol appears to increase. Another recently reported test (53) describes the enzyme *N*-acetyl hexosaminidase as a possible serum marker of rejection. Elevation of the level of this lysosomal enzyme occurs in cases of intestinal ischemia or necrosis and may be a useful marker for rejection.

Functional tests acquire special importance in the context of clinical SB transplantation, since Cs is used as an oral medication for clinical long-term immunosuppression. At the onset of rejection episodes, Cs absorption can be severely impaired, thereby accelerating the rejection process (54). Practical and sensitive functional tests would allow the prompt institution of antirejection therapy and the switching from oral to parenteral routes for delivering Cs to maintain adequate levels of the drug. On balance, a battery of functional tests may ultimately prove to be the solution to the accurate and timely detection of rejection episodes.

Summary

From this overview of the literature, it is clear that SB transplantation remains an experimental procedure and further studies are needed, particularly on more effective immunosuppressive regimens. The immunomanipulation of the recipient and/or combination therapies with monoclonal anti-T cell antibodies, as well as procedures to diminish the immunogenicity of the grafts, may be fruitful avenues of future investigation in SB transplantation. At present, although some studies provide reason for optimism, a number of technical, nutritional, and immunologic issues remain to be resolved before SB transplantation can be performed clinically with a reasonable degree of safety and with a prospect for long-term function.

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An Unexplained Peak of Pregnancy-Associated Thrombocytopenia

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Abstract

During the 3½ weeks July 18–August 12, 1985, an unusual incidence of pregnancy-associated thrombocytopenia was noted in the obstetric population of the Department of Obstetrics and Gynecology at Mount Sinai Hospital Medical Center of Chicago. Inquiries at some other Chicago area hospitals suggested possible similar peaks at two other teaching hospitals serving the same inner-city population as Mount Sinai.

Of 8 cases of thrombocytopenia at Mount Sinai during the 3½-week period, 6 were unrelated to any known underlying pathophysiology. Case 7 was immunologic thrombocytopenia, and case 8, EPH-gestosis-associated thrombocytopenia. Excluding cases 7 and 8, the incidence of thrombocytopenia for this period was 6%, whereas the incidence of recognized "unexplained" thrombocytopenia for the department in all of 1984 was ~.3% ($p < .001$), statistically a highly significant difference.

It is concluded that during July and August 1985 an unexplained peak of thrombocytopenia occurred in the obstetric population of the Department of Obstetrics and Gynecology at Mount Sinai Hospital Medical Center of Chicago and possibly also on the West and South sides of Chicago. This peak may have been caused by an infectious agent, since a majority of patients had a history of gastrointestinal symptoms. Various infectious agents are known to be capable of inducing antibodies cross-reactive with platelet membranes.

Thrombocytopenia can be caused by a variety of mechanisms (1–4, Table 1). In pregnancy, thrombocytopenia may also occur in association with preeclampsia or eclampsia (5, 6) and with what has recently been described as the HELLP syndrome (7). Considerable evidence has accumulated implicating platelet antibodies in the pathophysiology of thrombocytopenia associated with preeclampsia and with the HELLP syndrome (8, 9). Since assays for platelet antibodies have remained controversial, the data on antibody-induced thrombocytopenia are still contradictory (10).

The incidence of recognized antibody-induced thrombocytopenia, whether associated with preeclampsia or eclampsia (5, 6), the HELLP syndrome (7), or immunologic thrombocytopenia (ITP) (4), has remained low. The 6 cases of maternal thrombocytopenia we recognized in the period July 18–August 12, 1985 (6%)—none associated with preeclampsia, the HELLP syndrome, or known ITP—constitutes an incidence that is statistically highly unlikely to be due to chance. In 1984 only 4 such cases were seen in the department during a 12-month period (~0.3%). This difference is statistically significant ($p < .001$ by both chi square analysis and Fisher Exact test).

The 6 cases of thrombocytopenia are described here to alert physicians to the possibility that an antigen cross-reactive with platelet membranes may induce platelet-antibody-associated thrombocytopenia in pregnancy. Since an infectious agent may be the most likely culprit,

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TABLE 1
Causes of Thrombocytopenia

Defective platelet production
- Reduced thrombopoiesis
  - Marrow injury
  - Marrow failure
  - Marrow invasion
  - Thrombocytopoietin deficiency

Defective platelet maturation
- Vitamin B$_{12}$ deficiency
- Folic acid deficiency
- Heredity

Sequestration
- Splenomegaly
- Hypothermic anesthesia

Accelerated destruction of platelets
- Immunologic
  - Autoantibodies
  - Alloantibodies
- Nonimmunologic
  - Injury
  - Consumption
  - Hemorrhage

Adapted, with permission, from Eden RD, Platelet disorders (4).

this report is generated to encourage similar epidemiologic observations that would facilitate identification and isolation of any such agent.

Materials and Methods

To rule out undiagnosed autoimmune disease as a cause of thrombocytopenia, all sera from thrombocytopenic patients were investigated using previously described ELISA techniques (11) for the presence of a variety of autoantibodies usually present with autoimmune disease. These included antibodies to the phospholipids cardiolipin and phosphatidyl serine, total histones and histone subfractions H2A, H2B, H3, and H4 as well as polynucleotides ssDNA, dsDNA, Poly I, and Poly(dT).

To rule out classical ITP, the presence of platelet antibodies was also investigated. All platelet counts were initially obtained by an automated counter and later confirmed manually by an experienced hematologist. Platelet antibodies were detected by an indirect ELISA method described by Gudono and Miller (12).

All sera were obtained at platelet nadir and were frozen at −90°C until tested. Twenty normal pregnant patients served as controls for the establishment of a mean ±2 SD for abnormal platelet antibodies. Autoantibody test results were considered positive if the measured value exceeded 2 SD of 100 normal control sera.

Case Reports

Case 1. A 24-year-old black woman, gravida 3 para 1101, was initially admitted on July 18, 1985 at 31 weeks' gestation because of extreme bilateral breast enlargement and nodularities. Bilateral breast biopsies revealed benign hamartomas of both breasts. Her platelet count at that admission was 98 000 TH/mm^3; a repeat shortly thereafter was 89 000 TH/mm^3.

The patient was readmitted on September 11 at 39 weeks' gestation complaining about lower abdominal pain and diarrhea. Platelet count was 56 000 TH/mm^3. The patient was placed on hydrocortisone sodium succinate (Solu-Cortef), 200 mg i.v. every 8 h. Her platelet count increased to 97 000 TH/mm^3 on September 13. Against the advice of the perinatal physician, she underwent a cesarean section delivery on September 13. A male infant, Apgar score 9/10, weighing 2,990 gm, was delivered. Dubowitz score was comparable with 38 weeks' gestational age.

The infant's initial platelet count was 221-000 TH/mm^3, but fell to 86 000 TH/mm^3 by day 2 of life; thereafter the infant slowly recovered without therapy.

Mother and infant were discharged on postoperative day 7 in excellent condition. Maternal platelet count was 257 000 TH/mm^3, and the mother was slowly tapered off steroids.

Epidemiologic considerations: None.

Case 2. A 29-year-old black woman, gravida 2 para 1001, was admitted for observation on July 20, 1985 because of a suspicious nonstress test (NST) at 33 weeks' gestation.

The initial platelet count was 129 000 TH/mm^3. Repeated counts thereafter were all below 180 000 TH/mm^3. Although the initial lupus anticoagulant assay had been negative, a repeat was reported as clearly positive. Amniocentesis on July 25 revealed a mature L/S ratio, which led to induction of labor on July 27 after placement of cervical *Laminaria* on July 26. On July 28 a cesarean section was performed for suspected fetal distress, resulting in the delivery of a male infant, Apgar score 7 after 1 min and 8 after 5 min. The infant's weight was 2020 gm; Dubowitz scoring was 34–35 weeks.

Maternal platelets reached a nadir of 119-000 TH/mm^3 14 h after delivery and increased thereafter to 285 000 TH/mm^3 by postoperative day 5. At 3 and 6 weeks postpartum, counts were in a normal range. The neonate's platelet count was 269 000 TH/mm^3, and he was discharged at 12 days of age in excellent condition.

Epidemiologic considerations: The patient's brother was hospitalized for unknown reasons in June 1985.

Case 3. A 20-year-old black woman, gravida 3 para 1011, was admitted on July 23, 1985 at 37 weeks' gestation because of poor weight gain, urinary symptoms, and irregular contractions.

Her obstetrical history included a first-trimester loss and another spontaneous miscarriage at 20 weeks. A cervical cerclage was placed on May 11, 1985 when on initial prenatal visit her cervix was found dilated to 1–2 cm.

Her platelet count at the July admission was 163 000 TH/mm^3 but dropped to 117 000 TH/mm^3 within 24 h. L/S ratio was indicative of fetal lung maturity, and induction was started on July 26. At 3 cm dilatation a fetal scalp blood was obtained, revealing a fetal platelet count of 299 000 TH/mm^3. An outlet (Simpson) forceps delivery of a 2180-gm female infant occurred on the same day. Apgar score was 9 after 1 and 5 min. Dubowitz score of the infant was compatible with 38 weeks' gestational age.

Twelve hours postpartum, the maternal platelet count was 128 000 TH/mm^3; it fluctuated thereafter between 138 000 and 179 000 TH/mm^3 and reached 198 000 TH/mm^3 on postpartum day 4. Counts on day 12 were 279 000 and at 7 weeks postpartum 243 000 TH/mm^3.

Epidemiologic considerations: The patient reported nausea, vomiting, and diarrhea during the week prior to admission. In June she "permed" her own and a friend's hair.

Case 4. A 31-year-old black woman, gravida 8 para 1061, was admitted on July 24, 1985 at 20 weeks' gestation because of two successive episodes of syncope. Obstetrical history included one delivery at term, three induced first-trimester abortions, and three spontaneous pregnancy losses at approximately 20 weeks' gestation, each.

Six weeks prior to admission a cervical cerclage had been placed uneventfully. At that time (June 11) the patient's platelet count had been 220 000 TH/mm^3. Platelet counts during the patient's 5-day admission ranged between 146 000 and 167 000 TH/mm^3. After a negative medical workup, the patient was discharged for weekly follow-up. During the subsequent 6 weeks her platelets ranged from 150 000 to 190 000 TH/mm^3. The patient underwent normal vaginal delivery of a healthy infant at term. The newborn's platelet count was normal.

Epidemiologic considerations: The patient experienced one episode of nausea and vomiting with her second syncopal attack prior to admission. She was enrolled in a "beauty school" with exposure to a variety of chemicals on an almost daily basis.

Case 5. A 29-year-old white woman, gravida 1 para 0, was admitted on August 1, 1985 at 28 weeks' gestation with a major complaint of nausea, vomiting, and diarrhea lasting for 2 days.

Her medical history included a stapling operation for weight loss in 1982, which was successfully reversed in 1984, and a possible history of peptic ulcer disease.

The patient's medical workup during hospitalization, including stool cultures, was negative except for thrombocytopenia which fluctuated between 135 000 TH/mm^3 and 225 000 TH/mm^3. After discharge the patient was followed up twice weekly as an outpatient. Over the ensuing 5 weeks her platelets fluctuated between 187 000 and 215 000 TH/mm^3.

Owing to decreased fetal movements and questionable results on the nonstress test, the patient was induced and delivered on October 2 after fetal lung maturity was confirmed by amniocentesis. The newborn's platelet count was 384 000 TH/mm^3.

Epidemiologic considerations: The patient's presenting symptoms were gastrointestinal. Her mother experienced similar symptoms at the same time. The patient was exposed to rubber cement at work and had a "perm" applied to her hair in May 1985.

Case 6. A 21-year-old black woman, gravida 5 para 2113, was admitted on August 12, 1985 because of spontaneous rupture of membranes at an alleged gestation of 36 weeks. She had received no prenatal care and was an extremely unreliable historian. The obstetric history she recounted was that she had delivered three low-weight and/or premature infants.

The patient's platelet count at time of admission was 150 000 TH/mm^3. Shortly thereafter she went into spontaneous labor, which was augmented with oxytocin. On the day of admission she delivered a viable female infant by spontaneous vaginal delivery, Apgar score 9 at both 1 min and 5 min, who was growth-retarded (1,956 gm). Dubowitz score was compatible with 35 weeks' gestation.

Three weeks after delivery, the patient was readmitted to the hospital because of abdominal pain and postpartum depression. She denied nausea and vomiting but reported being constipated. Platelet count was 229 000 TH/mm^3, erythrocyte sedimentation rate was 82 mm/h, and white blood count with differential was normal. A positive gonorrhea culture was ob-

TABLE 2

Data on 8 Thrombocytopenic Mothers during Peak Period

Case no.	Lowest no. platelets per mm^3	ANA	Lupus anticoagulant	Circulating anticoagulant	GI symptoms	Comments
1	56 000	Negative	Borderline	Negative	Yes	Negative antiplatelet Abs
2	119 000	Negative	Positive	Intermittently mildly positive	—	ESR 66 mm/hr
3	117 000	Negative	Negative	Negative	Yes	
4	146 000	Negative	Negative	Negative	Yes	
5	135 000	Negative	Borderline	Negative	Yes	Negative stool cultures
6	150 000	Negative	Not done	Not done	—	
7	3 000	1:40 speckled	Positive	Negative	—	Diagnosis of ITP*
8	63 000	Negative	Positive	Positive	Yes†	EPH gestosis, possibly HELLP syndrome

* Patient underwent voluntary interruption of pregnancy after responding to corticosteroid therapy with increase in platelet count.

† Patient was seen 1 week prior to admission at another hospital complaining about nausea and diarrhea. She delivered at 28 weeks gestation a nonviable, 582-gm infant. IgG, IgM, IgA, and fibrinogen deposits were demonstrated by immunofluorescence in placenta.

tained, for which antibiotic therapy was instituted. The patient was discharged 3 days later and has remained well since.

Epidemiologic considerations: None.

In addition to these 6 cases of thrombocytopenia, 1 case of ITP (case 7) in early pregnancy was diagnosed during the same time period (platelet nadir 17 000 TH/mm^3) which resulted in therapeutic abortion at the patient's request. We also encountered 1 case of severe preeclampsia-associated thrombocytopenia (platelet nadir 63-000 TH/mm^3) during the period. The total incidence of thrombocytopenia was thus 8 of 99 deliveries (8%) during this period. In the summary of data for all 8 patients (Table 2) 5 of 8 patients reported gastrointestinal symptoms prior to admission.

Antibody Investigations

Except for antibodies to phospholipids, no significant antibody positivity was recognized in the 6 thrombocytopenic patients and 1 known patient with ITP (Table 3). Three of 6 thrombocytopenic patients and the ITP patient demonstrated either IgG or IgM antibodies to the two phospholipids cardiolipin and phosphatidyl serine. Antibodies to histones and nucleotides appeared only sporadically and were of no significance.

Platelet antibodies were detected in only 2 of 6 patients and in significantly high levels (+7 SD) only in the ITP patient. Interestingly, only IgG antiplatelet antibodies were detected.

Discussion

In 1979 Pitkin and Witte (13) demonstrated for the first time that even at term, platelet counts never fall to levels demonstrated in the cases reported here. Mean platelet counts for the three trimesters of pregnancy were 322 750 (first), 298 550 (second), and 300 870 (third) TH/mm^3. Their report was recently confirmed by another group of investigators (14), thus establishing that platelet counts of 150 000 TH/mm^3 are in the thrombocytopenic range at term.

This report is presented to alert to the possibility of an epidemic form of thrombocytopenia in pregnant mothers. The observation presented here is based solely on epidemiologic observations within one department of obstetrics. Oral communication with two other Chicago institutions suggested similar peaks at those institutions. In fact, at one of these Chicago teaching hospitals, two female health care providers were afflicted by "unexplained" thrombocytopenia in pregnancy. Unfortunately, despite repeated efforts, we were not given access to patient charts at either of these two institutions.

Our observation is supported by a similar observation made at Bellevue Hospital Center in New York City in a similar patient population during the same time of year (15). As in our experience, the Bellevue observation happened almost coincidentally and statistically could not have occurred by chance.

Possible Infectious Agent. What does this mean?

TABLE 3
Autoantibody Profiles

	Phospholipids			Histones, histone subfractions				Polynucleotides				
Case no.	CL	PS	TH	H2A	H2B	H3	H4	ss-DNA	ds-DNA	Poly I	Poly (dT)	Platelet antibodies
1 IgG	172*	111	107	119	108	93	57	60	77	118	130	Negative
IgM	177*	186	111	87	94	83	51	83	43	109	115	Negative
IgA	103	87	87	95	103	77	62	90	71	95	109	Negative
2 IgG	110	97	74	101	94	115	115	88	79	105	98	Negative
IgM	105	94	95	67	59	121	105	94	89	111	115	Negative
IgA	111	87	81	88	66	97	109	105	104	109	94	Negative
3 IgG	153*	107	56	105	77	101	107	120	117	112	121	+2.5 SD
IgM	159	149	97	109	89	117	119	141*	121	123	107	Negative
IgA	95	89	88	97	59	120	117	108	117	118	99	Negative
4 IgG	97	105	77	119	89	79	55	64	73	107	119	Negative
IgM	101	117	117	108	111	119	89	79	91	108	115	Negative
IgA	85	95	111	109	69	107	115	109	89	107	112	Negative
5 IgG	105	85	97	105	111	97	109	75	56	110	117	Negative
IgM	101	98	111	119	38	95	119	93	109	113	95	Negative
IgA	97	56	78	95	111	97	109	115	79	95	89	Negative
6 IgG	195*	205*	105	111	97	105	117	141	129*	93	155*	+3 SD
IgM	139*	195*	101	107	99	111	109	117	115	107	119	Negative
IgA	95	98	90	88	115	78	107	100	114	84	117	Negative
7 IgG	225*	238*	88	94	66	119	105	79	56	88	74	+7 SD
IgM	129	119	85	105	109	79	119	66	59	97	101	Negative
IgA	119	105	83	111	119	82	91	79	60	79	88	Negative

CL, cardiolipin; PS, phosphatidyl serine; TH, total histones.
* Denotes value above 2 SD over 100 control sera.

Cross-reactivity of autoantibodies is a well-recognized phenomenon (16). Antibodies to infectious agents, whether bacterial or viral, have repeatedly been demonstrated to induce cross-reactive antiplatelet autoantibodies (17–23). The concept that an infectious agent may induce an antibody that also binds to platelets therefore seems feasible. This antibody, like other platelet-associated antibodies, could then result in platelet destruction or speeded-up removal of platelets from the circulation (24, 25). Parvovirus-induced epidemics of aplastic crisis have been reported (26).

Five of the 8 patients we observed with thrombocytopenia, 4 of 6 with unknown etiology, had a clear history of gastrointestinal symptoms, including diarrhea and vomiting. This observation strongly suggests that the causative agent may affect gastrointestinal function. Bacterial and parasitic as well as viral agents can affect the intestinal tract (27). At least 1 family member, possibly 2, also suffered from gastrointestinal symptoms, strengthening the concept of a possible infectious agent. At this point such an agent remains, however, only a speculation.

The absence of evidence for polyclonal B-cell activation rules out the possibility of autoimmune disease as the underlying cause for the observed thrombocytopenia. Antiphospholipid antibodies have previously been reported in association with immunologic thrombocytopenia (28). However, the sparse detection of antiplatelet antibodies in the study group we investigated contradicts the possibility of classical ITP in these patients. Platelet antibodies are difficult to evaluate (10). The validity of our assay system was nevertheless supported by the fact that the single patient with proven ITP had by far the highest antiplatelet antibody titer in the series (Table 3). Since our assay system was developed to detect antiplatelet antibodies in ITP (12), its failure to detect platelet antibodies against a potentially different epitope is not surprising.

Association with Pregnancy. An additional question is why apparently only pregnant women were afflicted. Four explanations seem feasible:

- It is possible that pregnant women are more susceptible to the infectious agent involved.
- Alternatively, a pregnant patient's platelets could be more susceptible to the antibody.
- Or, third, the pregnant patient's reticuloendothelial system may be more capable of platelet removal once coated by antibody. Such a mechanism could, in fact, represent a mechanism protective of pregnancy, since an offending infec-

tious agent would be removed more rapidly from the circulation than usual. Interestingly, evidence has been reported that maternal platelet counts decrease toward the latter part of pregnancy (29). Recently an Australian group reported that (early) pregnancy produces a platelet-activating factor that may cause mild thrombocytopenia (30).

- The most likely explanation is, however, that nonpregnant individuals are usually not investigated—suggesting that the observed association with pregnancy represents, in fact, only a statistical bias.

Whatever the underlying cause, we believe that epidemiologic peaks of thrombocytopenia, as reported here and recently reported from New York (16), deserve further investigation in order to evaluate a possible infectious etiology.

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Perforation of the Esophagus: Experience at Bronx VA Hospital 1969–1984

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Perforation of the esophagus, in spite of numerous advances in surgical nutrition and other supportive techniques for past decades, still constitutes a true emergency and is associated with significant mortality (10–55%) (1–5). It has been regarded as "the most rapidly fatal and most serious perforation of the GI tract" (6, 7). Contamination of the mediastinum and often the pleural cavity with gastrointestinal fluids, food materials, and bacteria leads to sepsis and cardiopulmonary collapse (2). Immediate diagnosis and sound surgical judgment are demanded (8). Diagnosis, however, can be difficult because typical symptoms and signs may not be present and the usual diagnostic studies may fail to show perforation (2, 4). Being aware of the possibility of perforation of the esophagus is the most important element in making the diagnosis (9).

Immediate surgical intervention is usually needed, though some have advocated nonsurgical management in highly selected cases (10, 11). The type of operative management ranges from simple drainage to primary esophagectomy with an immediate reconstruction of the gastrointestinal tract (2–4, 12, 13).

In this paper we discuss our experience in perforation of the esophagus at the Bronx VA Medical Center for the years 1969–1984, with a focus on etiology and surgical management.

Materials and Methods

Operative reports between January 1969 and December 1984 were reviewed. A total of 21 cases of perforation of the esophagus were treated surgically in this period; perforations that occurred during the primary esophageal surgery, such as esophagomyotomy or esophageal anastomosis, were excluded. Six deaths occurred within 30 days after surgery (Tables 1, 2).

Etiology. Of 21 cases, 18 were due to iatrogenic causes. Upper gastrointestinal endoscopy was responsible in 12 of the 18 (7 rigid scope and 5 flexible scope). Six were in the cervical, four in the thoracic, and two in the abdominal esophagus. Two of four thoracic esophageal perforations by scope occurred during dilatation with graded metal olives. The other two occurred during biopsy. Two cases of perforation of the abdominal esophagus were most likely due to oversufflation of the esophagus with air. In all six cases of cervical esophageal perforation, passage of the scope itself was responsible.

In a group of patients undergoing paraesophageal surgery, vagotomy was responsible for all three abdominal esophageal perforations. One thoracic esophageal perforation occurred during right middle and lower lobectomy for bronchogenic carcinoma.

Two patients sustained cervical esophageal perforation by an endotracheal tube during intubation attempts in the Surgical Intensive Care Unit under suboptimal conditions.

One foreign-body perforation was caused by a double-edged razor blade in the cervical esophagus in a psychiatric patient. A case due to tumor was a patient who had left pneumonectomy for a lung cancer two years prior to his last and final admission to the hospital. He was admitted with cough and fever. Studies showed free perforation of the proximal esophagus into the left pleural cavity due to invasion of metastatic nodes. Spon-

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TABLE 1
Perforation of the Esophagus, 21 Cases

Pt. no.	Location	Cause*	Surgery	Result	Cause of death†
1	cervical	scope (R)	closure, drainage	lived	
2	cervical	scope (R)	closure, drainage	lived	
3	cervical	scope (F)	closure, drainage	lived	
4	cervical	scope (F)	closure, drainage	lived	
5	cervical	scope (R)	drainage only	lived; no laceration found	
6	cervical	scope (F)	drainage only	lived; no laceration found	
7	cervical	ET tube	drainage only	lived; possible pharyngeal perforation	
8	cervical	ET tube	closure, drainage	died	Original intraabdominal sepsis
9	cervical	foreign body double-edged razor blade	removal, closure, drainage	lived	
10	thoracic	scope (R)	cervical esophagostomy, rt. thoracotomy for drainage	died	Dilation for benign stenosis of distal esophagus. Diagnosis delayed a few days for minimal symptoms
11	thoracic	scope (R)	esophagectomy, cervical esophagostomy, gastrostomy, rt. thoracotomy	died	Ca of midesophagus; primary esophagectomy without reconstruction. Persistent mediastinal abscess
12	thoracic	scope (R)	rt. thoracotomy, (drainage), cervical esophagostomy	lived	
13	thoracic	scope (R)	closure & drainage	lived	
14	thoracic	spontaneous rupture from prolonged *Candida* sepsis	rt. thoracotomy, cervical esophagostomy, gastrostomy, ligation of GE	died	Massive GI bleeding 2 weeks after exclusion surgery
15	thoracic	tumor S/P left pneumonectomy (2 yrs) for bronchogenic Ca; developed esophago-left pleural fistula by metastases	gastric bypass	died	Bleeding from left subclavian artery after exclusion surgery
16	thoracic	lobectomy	closure & drainage	lived	
17	abdominal	scope (F)	closure & drainage	lived	
18	abdominal	scope (F)	closure & drainage	lived	
19	abdominal	vagotomy	closure & drainage	died	Vagotomy & hiatus hernia repair; died of continuing sepsis, despite immediate intraoperative repair
20	abdominal	vagotomy	closure & drainage	lived	
21	abdominal	vagotomy	closure & drainage	lived	

* R, rigid; F, flexible; ET, endotracheal tube.
† *Adapted from Contemporary Surgery.*

taneous perforation occurred in the patient who suffered from *Candida* sepsis following his total cystectomy for bladder cancer, small bowel fistula, and respiratory distress syndrome.

Surgical Treatment. Primary closure and drainage of cervical esophagus were performed in 5 of 9 patients when the actual laceration was identified. Drainage procedure only was performed in 3 cases, 2 due to endoscope and one due to endotracheal tube, when careful exploration failed to show perforation. In a case of foreign-body perforation, the foreign body (double-edged razor blade) was removed and primary closure of perforation with drainage of wound was performed.

Primary closure of perforation and drainage

TABLE 2
Mortality by Location and Etiology

Cause	Location			Total	Mortality by etiology
	Cervical	Thoracic	Abdominal		
Iatrogenic					
Scope	6	4	2	12	2
Paraesophageal surgery		1	3	4	1
Endotracheal tube	2			2	1
Foreign Body	1			1	
Spontaneous		1		1	1
Tumor		1		1	1
Total	9	7	5	21	6
Mortality by location	1	4	1	6	

of the right pleural cavity were performed for two patients. One patient was undergoing a dilatation attempt with graded metal olives for a benign stricture due to lye ingestion. In the second patient, the esophageal injury was noted during right lower and middle lobectomy for bronchogenic carcinoma. Two cases of perforation due to biopsy were treated with esophageal resection, cervical esophagostomy with feeding gastrostomy and drainage of the pleural cavity. These patients were diagnosed and operated on within 8 hours of perforation. One case of delayed diagnosis (case 10, Table 1) was treated with cervical esophagostomy, feeding gastrostomy, and drainage of the right pleural cavity. Similar procedures were carried out for a case of spontaneous perforation. A patient who developed perforation due to metastatic node (2 years after left pneumonectomy) was treated with substernal whole stomach bypass surgery.

All five patients with perforation in the abdominal esophagus were treated with primary closure and drainage of the area.

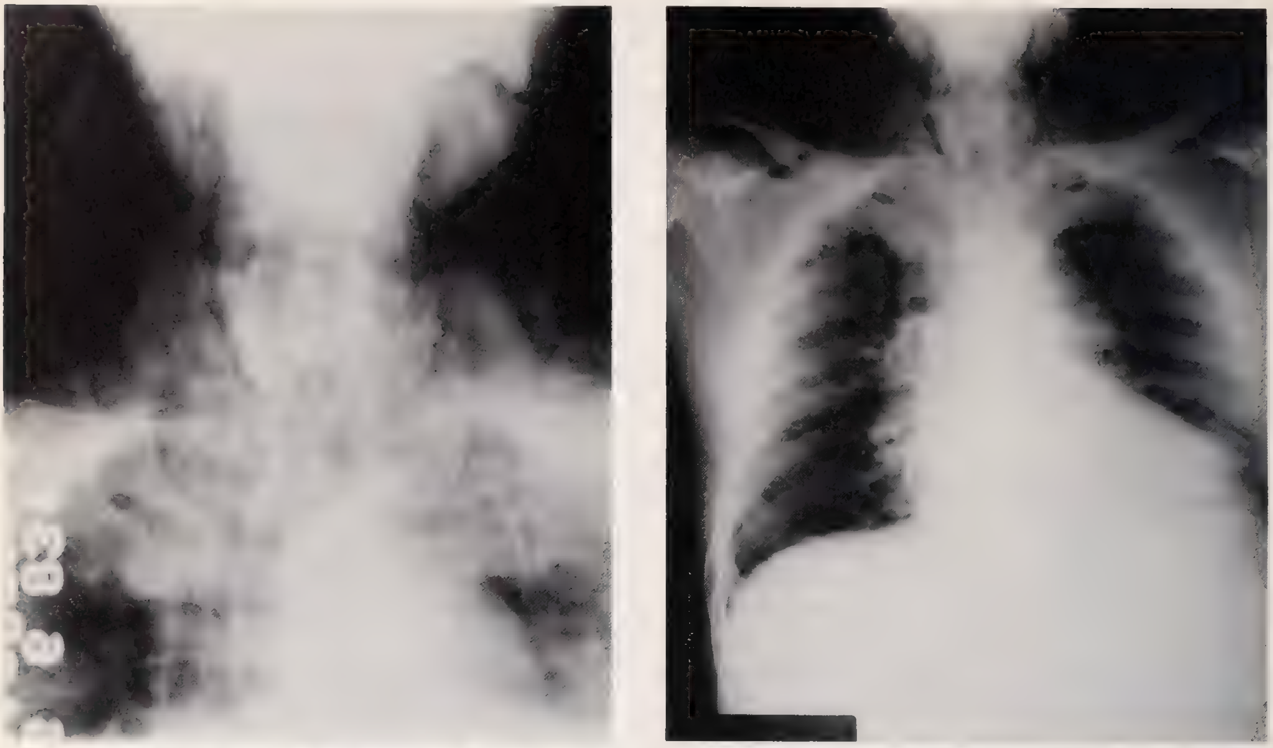
Mortality. The cause of each of the 6 deaths is summarized in Table 1. In 3, the basic condition of the patient, rather than perforation itself, was primarily responsible. The other 3 patients died of uncontrolled infection. In one patient, diagnosis was delayed one week because perforation was initially well-contained and symptoms were absent. The other two were diagnosed immediately and treatments were carried out without delay.

Representative Case Reports

An "Ideal" Case. A 66-year-old white man (case 3, Table 1) was referred to the Bronx VA Medical Center by LMD for neck pain following a flexible esophagoscopy for hiatus hernia, performed as an office procedure. During the procedure, the patient developed pain in his left neck and subcutaneous creptance. Upon admission to the hospital, an x-ray of the neck and chest showed typical subcutaneous emphysema (Fig. 1). An exploration of the neck from the left side was carried out within six hours of the incident. A one-cm laceration was found on the posterior wall of the cervical esophagus. Primary suture repair of the laceration and drainage of the wound were carried out, followed by an uneventful recovery.

Drainage of Wound Only. A 65-year-old white man (case 6, Table 1) underwent flexible esophagoscopy for reflux esophagitis. Shortly after the procedure, subcutaneous emphysema was noted. Gastrograffin swallow study was not conclusive but suggested perforation. Because of the typical clinical findings of perforation of the cervical esophagus, the neck was explored from the right side. No perforation was found. Exploration from the left side of the neck also failed to reveal the laceration of the esophagus or pharynx. Both

Indications for nonoperative management Contained perforation Minimal symptoms Minimal clinical sepsis	**Nonoperative treatment** Antibiotics I.V. Hydration (with or without T.P.N.) Nasogastric suction
Indications for operative management Pneumothorax Pneumoperitoneum Mediastinal emphysema Systemic sepsis Shock Respiratory failure	**Operative treatment** Drainage alone Suture repair (with or without flap) Primary esophagectomy Esophageal exclusion (with or without continuity) Endoesophageal intubation



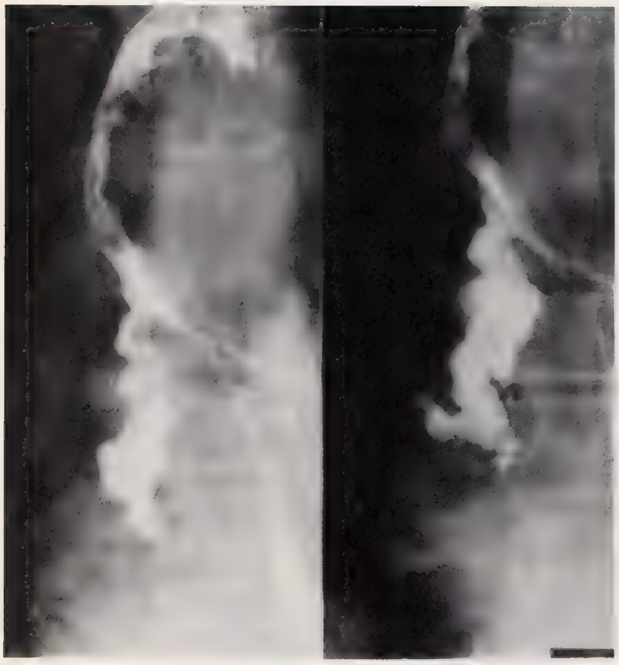
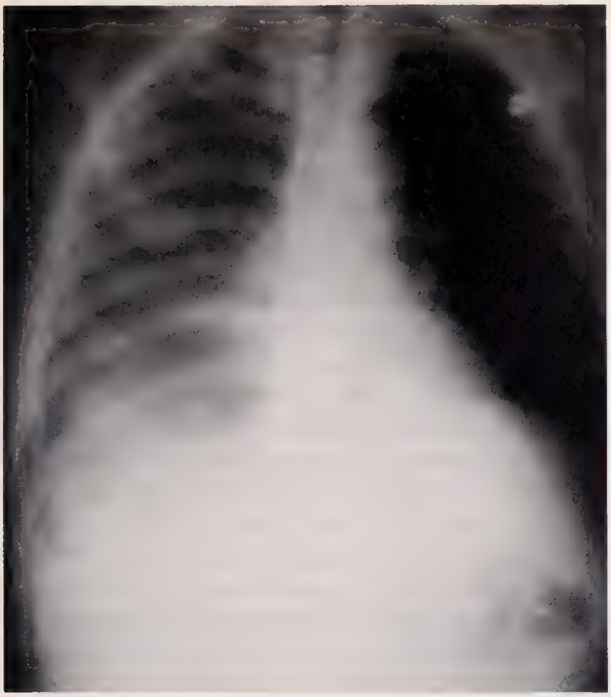


Fig. 1. **Case 3, Table 1.** Neck film (**left above**) and chest film (**right above**) showing subcutaneous emphysema. *Courtesy of Contemporary Surgery.*
Fig. 2. **Case 11, Table 1.** Esophagogram showing perforation. *Courtesy of Contemporary Surgery.*

wounds were drained. The patient had an uneventful recovery.

Perforation during Biopsy. A 65-year-old black man (case 11, Table 1) with a fungating midesophageal carcinoma underwent a rigid esophagoscopy with biopsy under general anesthesia. The patient developed fever and complained of right chest pain immediately after the procedure. An emergency esophagogram showed a perforation of the esophagus, 4 cm above the tumor (Fig. 2). Emergency surgery, consisting of feeding gastrostomy, esophagectomy, cervical esophagostomy, tracheostomy, and drainage of mediastinum was performed. About 2500 cc of foul-smelling fluid was evacuated from the right pleural cavity. Time between the scope and surgery was 8 hours. His postoperative course was complicated by persistent infection, which devel-



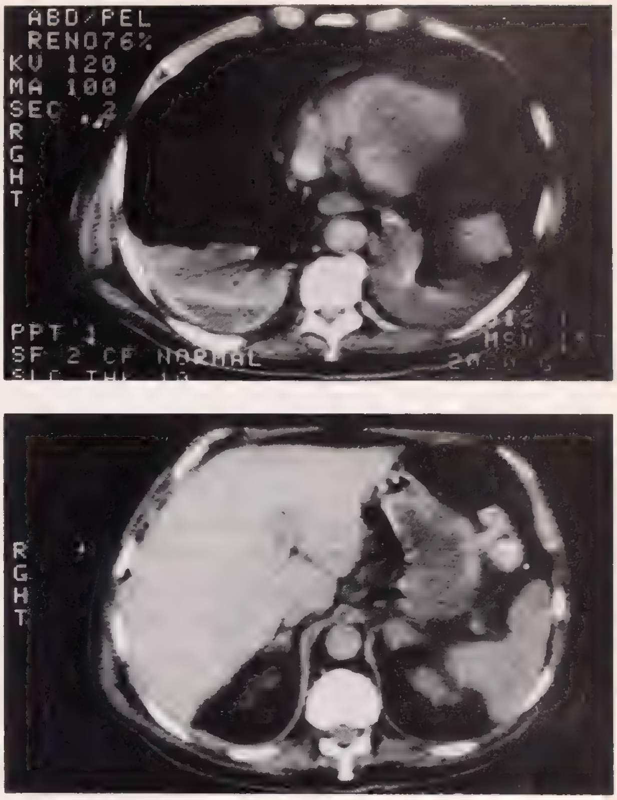


Fig. 3. Case 14, Table 1. Left Chest film showing pleural effusion. **Fig. 4. Right** CT scan showing air in the lesser sac and mediastinum. *Courtesy of Contemporary Surgery.*

oped into the mediastinal abscess. This abscess was drained 3 weeks after the original surgery. The patient died shortly thereafter.

Perforation Distal to Stenosis. A 47-year-old Indian man (case 13, Table 1) accidentally ingested lye a year and a half prior to the incident under study. He developed a typical stricture of the esophagus and underwent several dilatations. During one of the dilatations with a metal olive, perforation of the mid-portion of the esophagus was suspected; immediate gastrograffin study confirmed perforation of the midesophagus just distal to the stricture itself. Right thoractomy was performed. Primary repair of the perforation and drainage of the right pleural cavity was carried out. The patient had an uneventful recovery. He eventually underwent left colon bypass surgery sometime later.

Multiple Causes of Death. A 58-year-old white man (case 14, Table 1) underwent a total cystectomy with an ilial conduit for urinary bladder carcinoma. Three weeks postoperatively, the patient developed a pelvic abscess, which was drained by laparotomy, followed by small bowel fistula and *Candida* sepsis. Intensive treatment with TPN, oral feeding, and amphotericin B were given. About two months after his original surgery and two weeks after his latest abdominal surgery, he developed fever, nausea, and vomiting, which subsided without any specific treatment. A chest film at this time was reported as normal. Twenty-four hours later, massive right pleural effusion was noted (Fig. 3) and a chest tube was inserted. Over 2000 cc of purulent fluid was drained. He continued to drain several hundred cubic centimeters of pus daily and remained very ill. Amylase of pleural fluid was 1600 units. CT scan of abdomen and chest showed the presence of air in the lesser sac and mediastinum (Fig. 4). The patient was taken to the operating room one week after the development of right pleural effusion, and an exploratory laparotomy was carried out. No perforation of intraabdominal organ was noted. Therefore, a right thoracotomy was carried out. Perforation of the distal esophagus just above the hiatus at the right posterior lateral wall was noted. Ligation of the GE junction, feeding gastrostomy, and endcervical esophagostomy were carried out. He recovered from this episode fairly well but died three weeks later due to massive upper gastrointestinal bleeding.

Discussion

Etiology. Perforation of the esophagus has various causes. In the literature as well as in our experience, iatrogenic causes lead the list; they

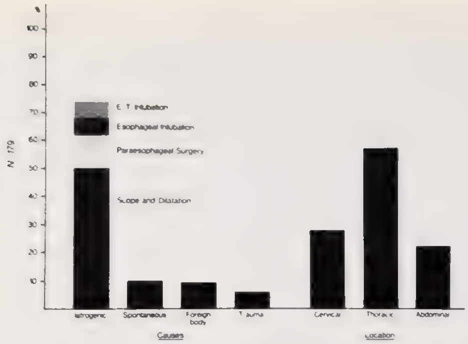


Fig. 5. Causes and location of perforation of the esophagus. Review of Bronx VA Medical Center experience January 1969–December 1984 (see Table 1) and 3 series from literature (4, 7, 8). *Courtesy of Contemporary Surgery.*

cause about 70% of all perforations (1, 7, 12) (Fig. 5). Among the iatrogenic causes, upper gastrointestinal endoscopy is the most frequent (4, 7, 12). There appears to be no significant difference between the rigid and flexible scope (14, 15). Endoscopic dilatation of the esophagus carries a greater risk than endoscopy alone (16, 17). According to a 1974 American Society for Gastrointestinal Endoscopy survey (16), upper gastrointestinal endoscopy entailed a perforation rate of only 0.03% (70 of 211,410), whereas esophageal dilatation (all types) entailed a rate of 0.25% (59 of 23,794). In the dilatation group, the risk increases according to the modality used. With mercury bougies, the risk of perforation was 0.09%, with metal olives 0.35%, and with pneumatic or mechanical methods 1.4%. Perforation usually occurs in the diseased thoracic or abdominal esophagus during the dilatation (18). Forceful hydrostatic or pneumatic dilatation for achalasia carries a fairly high perforation rate of 4% (17, 19). The second most common iatrogenic cause is para-esophageal surgery, such as vagotomy, hiatus hernia repair (20, 21) and pulmonary surgery, e.g., radical pneumonectomy (22).

Our experience is no exception. The overall incidence of iatrogenic perforation of the esophagus at the Bronx VA Medical Center was 18 of 21 cases (86%). Upper gastrointestinal endoscopy was responsible in 10 cases, 6 in the cervical, 2 in the thoracic, and 2 in the abdominal esophagus. Two thoracic esophageal perforations were caused by biopsy. All cervical perforations were due to instrument passage; 2 cases of the abdominal perforations were most likely due to insufflation of the distal esophagus with air. Attempts at dilatation of benign stricture of the esophagus were responsible in 2 cases of thoracic esophageal perforation.

All 3 instances of abdominal esophageal perforation secondary to para-esophageal surgery were truncal vagotomy cases. Two additional cases of tear of the seromuscular layer without damage to the mucosa were reported in this period. These injuries usually occurred during attempts to isolate the esophagus. One case of thoracic esophageal perforation during lower and middle lobectomy of the right lung occurred in the process of mediastinal lymph-node dissection as reported in the literature (22).

Traumatic endotracheal intubation may cause injury to the hypopharynx area or cervical esophagus. This type of injury is usually associated with a blind thrust or with poor exposure (23). Both cases of our series had a few intubation attempts in the Surgical Intensive Care Unit under suboptimal conditions. This particular complication of attempted endotracheal intubation has rarely been reported.

Other causes of iatrogenic perforation not encountered in our series include endoesophageal intubation, esophageal obturator airway, esophageal balloon tamponade, and nasogastric (Levin) tube. Endoesophageal intubation, either of the pulsion or traction type, can cause a perforation during the procedure or as a postoperative complication (24, 25). Esophageal obturator airway for CPR by EM technicians is a useful tool but is also associated with a risk of esophageal perforation (26). Sengstaken-Blakemore and similar balloon tamponade tube can damage the esophagus by prolonged pressure on its wall or by technical problems, such as an improperly placed stomach balloon (18). Even a simple Levin tube can cause perforation (27).

Spontaneous perforation, also known as Boerhaave's syndrome, was first reported by Boerhaave in 1724 and reviewed by Barret in 1946 (28). This usually occurs following severe vomiting. The mechanisms involved are (a) increased intraluminal pressure; (b) preexisting disease; and (c) neurogenic factors (5, 18, 29). One case of spontaneous perforation in our series is not a clear-cut case of this entity because many factors contributed to the perforation of the patient's esophagus, including *Candida* infection, previous history of nasogastric intubation, nausea, and vomiting. However, there was no intervention immediately prior to the episode except a few episodes of vomiting. Therefore, spontaneous perforation is most likely.

A wide variety of foreign bodies, accidentally or intentionally introduced, are another cause of perforation. Ballpoint pens, razor blades, coins, animal bones, safety pins, and dentures are just a few of the objects that have been reported. The foreign bodies themselves can be the direct cause of perforation, or attempts to remove these objects may cause the injury (30). In our case, the diagnosis of perforation of the cervical esophagus was made preoperatively but the cause was unknown until a double-edged razor blade was found during surgery; no history was obtainable because of the patient's psychiatric problem, and all x-ray films failed to show a metallic object. Perforation due to external trauma, either sharp or blunt, is fairly uncommon (except in the cervical esophagus) because of anatomic location. An isolated injury to the esophagus, especially by blunt trauma, is rare. Most of the injuries are associated with damage to the surrounding structures (31, 32).

Tumors, either primary or secondary, rarely cause free perforation, but may cause a localized mediastinal abscess, or a fistula to the tracheobronchial tree. At the Bronx VA Medical Center, several cases of localized abscess formation due to either bronchogenic or esophageal cancer were seen, but the single case in our series was the only incident of free perforation of esophagus due to a tumor.

Diagnosis. The most common symptoms and signs are chest pain and crepitus. Fever, tachycardia, dyspnea, and leukocytosis may be present (2, 4, 7, 12). Plain films of the neck, chest, and abdomen may show subcutaneous emphysema, pneumomediastinum, widening of the mediastinum, pleural effusion and pneumoperitoneum (2, 4, 6, 7, 12). An esophagogram with contrast medium may localize the point of perforation and extent of injury (33). There is some dispute over whether barium or iodinated water-soluble compounds should be the medium of choice, although barium gives superior visualization (33). A positive esophagogram is seen in about 75% of cases (7, 8). CT scan of the chest may show air in the mediastinum (Fig. 5). The patient may not complain of pain until fully awake if the procedures are done with the patient under general anesthesia (24). Symptoms and signs are nonspecific. A suspicion of perforation of the esophagus is the most important element in making the diagnosis.

Treatment. As a rule, operative treatment is indicated unless a specific reason for nonoperative management is present (4). The decision depends on wound location, time interval, cause, and general conditions (see box). In either case, intravenous hydration, antibiotics, and nasogastric suction should be started as soon as the diagnosis is made (9). Insertion of a nasogastric tube can be difficult, and extreme care must be taken not to cause further damage to the esophagus. The type of operative management (see box) ranges from simple drainage to primary esophagectomy with an immediate reconstruction of the gastrointestinal tract (2–4, 12, 13).

For a perforation of the cervical esophagus, suture closure is desirable if it can be done easily, but it is not essential. Simple drainage is satisfactory (2, 3, 9). In our experience, 6 of 9 cases (including a case of perforation due to a foreign body), the injury was identified and suture closure and drainage were done. In 3 cases, no injury could be identified and drainage alone was performed. All of these patients did well, except for a patient suffering from perforation due to traumatic endotracheal intubation who eventually died of his original intraabdominal sepsis.

For the abdominal esophagus, suture repair with omental reinforcement or the Thal procedure can be used (3, 4, 12). All 5 patients in this series received primary closure with omental reinforcement.

For the thoracic esophagus, the choice of treatment depends on the situation. The most important principle is the establishment of satisfactory drainage and prevention of further contamination (2). Suture repair and mediastinal drainage can be done without thoracotomy by a posterior approach (24). In the majority of cases, however, a thoracotomy is necessary. This facilitates debridement and drainage of the pleural cavity (9). If the patient is seen early, suture repair of the perforation can be done with or without pleural or diaphragmatic pedicle flap (12). If the perforation is proximal to a stenosis, for example cancer of the distal esophagus, primary esophagastrectomy with anastomosis may be considered (13), or the establishment of the gastrointestinal tract can be done at a second stage. Exclusion and diversion surgery such as cervical esophagostomy with or without continuity and feeding gastrostomy and ligation of the GE junction are some of the commonly used techniques (3, 35). In our series, 2 patients were treated with primary closure of perforation with chest tube, 2 with esophagectomy, cervical esophagostomy, and feeding gastrotomy, one with substernal gastric bypass, and one with cervical esophagostomy, feeding gastrostomy, ligation of GE junction, and drainage of right pleural cavity. Endoesophageal intubation is also a useful technique in certain situations (24, 25). At the Bronx VA Medical Center, this modality was applied to the patients with tracheobronchial fistula, but no patient with perforation of the esophagus was treated with this technique.

It is essential to start the treatment as soon as possible because delay in treatment is associated with higher mortality (3, 7). The value of total parental nutrition is not well-established (4, 31) but is probably useful postoperatively in the depleted patient.

Mortality. The mortality ranges from 10% to 55% in the recent literature, without significant changes for the past 20 years (1–5). Time interval between perforation and the beginning of the treatment, location of perforation, etiology, and original condition of the patient seem to be the important factors affecting mortality and morbidity (3, 4, 7). If the start of treatment is delayed more than 24 hours, mortality is significantly higher. Foster reported 43% mortality when the delay in treatment was more than 24 hours, and only 13% mortality if treatment was started in less than 24 hours (7). Michel reported similar experience (28.6% vs 11%) (4). A report from MGH showed 0% mortality in a group of patients whose perforation was caused by foreign body or external trauma, whereas the groups with iatrogenic and spontaneous perforations sustained 21% and 22% mortality (4). The importance of the location of perforation and underlying general conditions is clear in the literature (3, 4, 7) as well as in our own experience. Of the six patients in this series who died, three died because of underlying disease or its related complication rather than perforation per se. The other 3 deaths were directly related to perforation; one (thoracic perforation) had a delayed diagnosis of one week, and two (abdominal perforation and thoracic perforation) died of uncontrolled sepsis secondary to perforation itself.

Summary

Perforation of the esophagus remains one of the most serious gastrointestinal tract perforations and is associated with significant mortality. An iatrogenic cause is the most common and comprises 70% of all perforations. Surgical intervention is indicated in most of the cases. Various types of surgeries are described. In the Bronx VA Medical Center, a total of 21 cases of perforation of the esophagus with 6 deaths were seen in the 16 years from January 1969 to December 1984. Etiology and surgical treatment of these patients, as well as the literature, are reviewed.

Acknowledgments

All tables and all figures in this article contain material that has been adapted with permission from Sakurai H. Perforation of esophagus, etiology and treatment. Contemporary Surgery (in press).

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Medical Cost Containment: A Daily Patient Log Sheet to Reduce Unnecessary Hospitalization

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Abstract

In a prospective study of two medical wards at The Mount Sinai Hospital, an administrative intervention was instituted in an attempt to modify physicians' use of medical services. A daily log sheet was placed on each patient's chart on the study ward, and house officers were instructed to document the justification for each hospital day. Daily review of charts of all patients on the two wards determined the necessity for hospitalization, using the criteria of the Peer Review Organization. The percentage of unnecessary days of hospitalization on the study ward was 8% (28/363) and 18% (65/363) on the control ward ($p < 0.05$). The mean number of patients with unnecessary days of hospitalization was 12 (21%) on the study ward and 20 (32%) on the control ward ($p = 0.15$). Placement of a daily log sheet on medical charts is a simple, feasible, and effective method. It offers the potential for more appropriate utilization of hospital days and thereby avoidance of fiscal losses associated with retrospective denials by PRO.

Much attention has focused on developing programs to control escalating health care costs. Physicians play an important role in generating these costs, and various attempts have been made to induce physicians to participate in cost containment (1). The Peer Review Organization (PRO) was recently established to modify physicians' use of hospital resources and limit expenditures. PROs retrospectively review the services provided to Medicare patients to ascertain whether they are medically necessary and therefore eligible for reimbursement (2). The Mount Sinai Hospital has instituted an internal Utilization Review Committee to prospectively detect the unnecessary use of medical services. Its purpose is to minimize the subsequent disallowance of hospital days by the PRO.

In an effort to further limit unnecessary use of the hospital, we added a daily log sheet to medical charts for documentation of the reasons for each day of hospitalization. We studied the effect on physician behavior of focusing attention in this manner on the issue of proper utilization.

Methods

We performed a prospective controlled study on two parallel medical wards at The Mount Sinai Hospital, New York City, for a two-week period. The study ward was chosen to be two south of the Klingenstein Clinical Center. The control ward was two north. Each ward consists of 42 acute medical beds. Patients are admitted to each medical ward without regard to diagnosis or problem. Ward teams consist of one third-year resident, three interns, and two subinterns. Interns and subinterns are responsible for writing all routine orders, including those for diagnostic tests, and can discharge service patients. Attending physicians write the discharge orders for private patients. The two wards chosen share the

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TABLE 1
The Effect of the Administrative Intervention on the Two Patient Population

	Study ward	Control ward
	No. (%)	No. (%)
Days denied/reviewed	28/363 (8)	65/363** (18)
No. pts with denied days	12 (21)	20 (32)
Status		
Private	5 (42)	16* (80)
Service	7 (58)	4 (20)
Age		
Under 65 yrs	9 (75)	8 (40)
65 and over	3 (25)	12* (60)
Mean no. days denied per pt	.49 ± 1.72	1.05 ± 1.97*

* $p \leq 0.05$
** $p \leq 0.025$

same hospital floor, but are staffed by different nurses. Interns and subinterns do not cross from one team to another. Attendings, however, can admit to both wards.

On the first day of the study a log sheet, the administrative intervention, was placed on the front of every chart on the study ward and on the chart of every patient subsequently admitted to that ward. Interns and subinterns were instructed by the investigators at one five-minute meeting to write the date and specific care the patient received which necessitated each day's hospitalization. They were not informed about how this information would be used. The log sheets were collected on the patient's discharge, transfer, or death and were not evaluated until the end of data collection.

General information on each patient, such as demographic facts, admitting diagnosis, and reason for admission, was collected on both the control and study wards. Daily chart review was performed using *Screening Criteria for Short Stay Hospital Review,* a supplement to the New York County Health Services Review Organization Criteria (3). This book lists diagnoses and specific criteria which must be documented to justify reimbursement. If the reason justifying a hospital stay could not be determined from the chart, that stay was recorded as an unnecessary day. When charts were encountered in which whether a day was justified was uncertain, physician advisors of the Mount Sinai Quality Assurance Utilization Review Committee were consulted. Student's *t*-test and chi-square test were used in the statistical analysis of the results.

Results

There was an 80% daily compliance rate among house officers, and 79% of the completed sheets were filled out correctly according to the instructions given on the first day of the study. The 74 days that were not accounted for by a physician on the log sheet would have been justified in 85% of the cases. Noncompliance was not due to physician absence. During the two-week study period, the medical team on the study ward cared for 57 patients and the control ward for 62 patients. A total of 363 inpatient days were reviewed on each ward.

More days were denied, and a larger mean number of days were denied, per patient on the control ward (Table 1) than on the study ward ($p < 0.05$). The difference in total number of patients with denied days on study and control wards was not significant ($p = 0.15$).

The percentage of private patients with denied days on the study ward was less than on the control ward ($p < 0.05$) (Table 1). However, there was no signficant difference in the percentage of service patients with denied days when the two wards were compared (Table 1). The number of patients 65 years and over with denied days was significantly greater on the control ward ($p < 0.05$) (Table 1). This was not found among patients under 65 years when comparing both wards.

The percentage of patients in each diagnostic category was similar on both wards except for the cases with neurologically related diseases. However, the neurology cases on the control ward did not have a greater than expected percentage of denied days (Table 2).

Discussion

Numerous programs have focused on changing physicians' use of medical resources in order to contain health care costs (1). Use of a log sheet to document the daily need for hospitalization can minimize unnecessary hospital stays and limit the hospital's fiscal liability. According to the present peer review system, denied days are not reimbursable. Thus, the 42 denied days on the control ward that exceed the number of denied days on the study ward represent a potential cost to the hospital of approximately $24,000. With the advent of hospital reimbursement on the basis of diagnosis-related groups (DRGs), the cost to the hospital might have been greater. As indicated from our study, if more attention were given to more efficient use of hospital days, this signficant sum of money might have been saved.

The comparison of the number of denied days may have overestimated the difference between the two wards by considering multiple denied days for a patient as independent data points. When the number of patients with denied days on the two wards was compared, there was no significant difference, but the results suggested the same trend. A small patient population may explain these findings.

Our method of intervention appears to have had a greater impact on the management of private patients and patients aged 65 years or over. Although house staff completed the daily log sheet, the smaller number of private patients with denied days on the study ward suggests that the influence of the intervention may be greater on attending physicians. Physicians generally have more flexibility with private patients. Outpatient work-ups and early discharge are more feasible because of more extensive family and financial support systems. Private physicians are often more aware and may be more directly affected by pressure from the peer review system. At the time of the study, a series of sanctions had recently been instituted against private physicians whose use of hospital days was found to be inappropriate by the Utilization Review Committee.

Other studies have successfully used administrative changes to alter the use of hospital resources. Griner demonstrated a decrease in laboratory testing in association with combined educational programs and administrative changes (4). Dixon and Lazlo limited residents to eight tests per patient and showed that laboratory use became more selective with a 25% reduction in testing (5). Most studies involving an administrative method of intervention have been used to alter the test ordering behavior of house officers. We have demonstrated that this strategy for changing physician behavior and controlling costs may have a broader application. Hospital care accounts for 41% of health care costs; influencing physicians to eliminate unnecessary hospitalizations and hospital days would have a substantial impact on cost containment (6).

Seventy-nine percent of the completed daily log sheets were filled out correctly with a valid therapeutic or diagnostic reason for hospitalization documented daily. This suggests that the majority of house staff on the study ward appear to have the proper knowledge and training to understand the appropriate criteria and indications for hospitalization. This may not be representative of all medical house officers, because the sample studied was small and the sampled house officers' baseline knowledge about the criteria for hospitalization was not defined in comparison to other house officers. Physician utilization of hospital resources is determined by a number of factors, including knowledge of costs, financial incentives, and medical training. Our results indicate that there is room for improvement in the amount of knowledge physicians posess in regard to understanding the appropriate criteria for hospitalization. Educational programs aimed at changing physicians' use of hospital resources and encouraging cost-effective behavior have been studied (1). These programs have been successful, but their long-term impact is questionable. There does appear to be a need for developing strategies to provide medical staff with the information they need to make appropriate use of hospital facilities.

TABLE 2

Description of Patient Populations on Study Ward and Control Ward during Administrative Intervention

	Study ward (N = 57) No. (%)	Control ward (N = 62) No. (%)
Status		
Private	34 (60)	43 (69)
Service	23 (40)	19 (31)
Age		
Under 65 yrs	34 (60)	30 (48)
65 and over	23 (40)	33 (53)
Mean age	57	63*
Mean no. days patient followed	6.3	5.9

* $p \leq 0.05$

Our method of intervention is simple and feasible to introduce. It requires a small commitment of time by the house staff and incurs no cost to the hospital. In this era of dramatic attempts at outside intervention to reduce hospital expenses, such a log sheet should work from within the medical system to aid cost containment. With the advent of hospital reimbursement based upon a specific number of days per "disease-related group," the need for appropriate utilization of each hospital day will become more important. This can be accomplished with the use of organized record-keeping systems, peer review, and daily log sheets such as we have proposed. The results demonstrate that encouraging physicians to carefully consider and document the reason for each inpatient day, in addition to prospectively evaluating patient management, may be an effective method of containing costs.

Limitations of the Study. The daily patient log sheets were anonymous. Therefore, the characteristics of compliers and noncompliers could not be evaluated. Every patient log sheet had at least two days of documentation; thus no one physician was entirely noncompliant. The reasons for compliance on one day and noncompliance on others were not assessed.

Another limitation of the study is the small number of patients and physicians. Studying a larger population of both physicians and patients would make it possible to define specific patient cases at higher risk for having days denied and physicians whose practice patterns result in a larger than expected number of nonreimbursable hospital days.

A more extensive randomized control study is necessary to address these questions and to assess the long-term efficacy of this intervention.

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Diltiazem-Associated Immune Thrombocytopenia

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Abstract

I describe here the first reported case of immune thrombocytopenia in a 68-year-old man taking diltiazem for unstable angina and quinidine and digoxin for other disorders. The association of thrombocytopenia is based on the following. Thrombocytopenia was most closely associated by history with the introduction of diltiazem into the patient's regimen, and platelet count recovery occurred after its discontinuation. Nonimmune causes of thrombocytopenia were excluded as etiologies on a clinical basis. Peripheral smear, bone marrow aspirate, and in vitro assays of antiplatelet IgG were consistent with an immune etiology of thrombocytopenia. Serum drug-dependent antiplatelet antibody assay supported diltiazem as the cause. This patient was also given morphine, diazepam, isosorbide dinitrate, intravenous nitroglycerine, quinidine, lidocaine, digoxin, hydroxyzine pamoate, furosemide, and warfarin during his hospitalization. These drugs either did not meet the clinical criteria for drug-induced thrombocytopenia, or were excluded on the basis of serum drug-dependent antiplatelet antibody findings. From these data it was concluded that diltiazem caused the patient's thrombocytopenia.

Diltiazem HCl (Cardiazem, Marion Pharmaceuticals) is a slow calcium channel blocker currently used in the treatment of angina. Herein is described a case of drug-induced immune thrombocytopenia in a 68-year-old man while he was being treated with diltiazem and other drugs for unstable angina.

Clinical History

A 68-year-old man was admitted to hospital in August 1983 after one week of increasing frequency and severity of angina. He had a long medical history, beginning with Buerger's disease in 1946, which resolved with cessation of smoking. An anginal syndrome developed in the late 1960s. He had anteroseptal wall infarctions in April and July 1974 complicated by Dressler's syndrome and ventricular aneurysm. Another anterior wall infarct in January 1975 was complicated by runs of ventricular tachycardia suppressed by Pronestyl. Thrombophlebitis in July 1975 and pulmonary embolus in May 1976 were treated with anticoagulation therapy. He had several hospitalizations for chest pain from 1976 to 1983. Maintenance medications included nitrates, digoxin, Lasix, Valium, and antiarrhythmics for a stable anginal syndrome, ventricular arrhythmias, and mild congestive heart failure. Laboratory examination during these years showed normal white blood cell and platelet counts, normal hemoglobin, and therapeutic anticoagulation.

Examination on admission in August 1983 was notable only for bibasilar rales and chronic lower-extremity venous stasis changes without edema. Electrocardiogram was unchanged from previous records and showed normal sinus rhythm with first-degree atrioventricular block, old anteroseptal infarct, and ventricular aneurysm. Chest x ray was unremarkable. Admission laboratory results hemoglobin 15.7 gm/dL; white blood cells 6,900/mm^3; platelets 178,000/mm^3;

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prothrombin time 25 sec; partial thromboplastin time 62 sec.

Hospital Course. Drug therapy started on the first hospital day included morphine, diazepam, isosorbide dinitrate, and diltiazem for the unstable angina; quinidine was continued for ventricular ectopy. Digoxin use was continued, and furosemide and warfarin use were discontinued. Cardiac isoenzymes were not present, but continued chest pain and changes in ST-T waves required intravenous nitrate therapy and hemodynamic monitoring.

The patient's platelet count began to decrease after hospital day 3 and was less than 100,000 by day 17, whereupon quinidine, diazepam, and diltiazem were withdrawn. (Isosorbide dinitrate or intravenous nitrates were continued because of clinical necessity.) Hydroxyzine pamoate and lidocaine were substituted. The platelet count reached a nadir at 39,000 on hospital day 23; the count was 100,000 by day 27, and 314,000 by discharge. The patient's anticoagulation therapy was resumed late in his hospital course, first with pork heparin, then with warfarin; neither drug affected the platelet count. Quinidine use was also cautiously restarted late in his course because of the need for arrhythmia control and previous lupuslike reaction to Pronestyl: the quinidine had no effect on platelet recovery. The drugs prescribed for the patient at discharge were warfarin, isosorbide dinitrate, quinidine, and hydroxyzine pamoate. Blood counts were normal at 2 weeks and 5 months after discharge.

Methods

Peripheral smear and Wright-stained bone marrow aspirates were examined by standard techniques.

Samples of patient serum and platelets were obtained on hospital day 17 (the day when the patient developed clinical thrombocytopenia of less than 100,000), as well as 4 and 5 months after discharge. They were assayed for platelet-associated antibody, serum antiplatelet antibody, and drug-dependent antiplatelet antibody using a solid-phase radioimmunoassay developed at this institution by Hymes et al (1) and Faig and Karpatkin (2). The methods are briefly recounted below.

Platelet-Associated IgG. A total of 10^7 washed platelets from the patient and a similar sample from normal controls were assayed for immunoglobulin by allowing platelets to adhere to the wells of a plastic 96-well microtiter plate, washing, then adding 40 μl rabbit antihuman IgG at 1:80 dilution to each well. After rinsing, 40 μl of ^{125}I-staphylococcal protein A, or the equivalent of approximately 150,000 counts per minute, was added to each well. The samples were incubated 1 hr at 27°C and rinsed, then each well was individually cut out and assayed for radioactivity. Results were expressed as mean count per minute of triplicate assays of the patient's platelets divided by control platelets. Results were then quantified by plotting data on a standard IgG curve as described by Hymes et al (1). Normal values are 2.81 ng/10^7 platelets; 2 standard deviations = 1.2.

Serum Antiplatelet IgG. A total of 10^7 washed control platelets was allowed to adhere to wells of a plastic microtiter plate. Forty microliters of serial dilutions of serum from the patient or normal control in 1% bovine serum albumin–phosphate buffered saline was added to each well. After washing, 40 μl of ^{125}I-staphylococcal protein A was added to each well and incubated 1 hr. The wells were rinsed and assayed for radioactivity as described above. Results were expressed as a mean ratio of counts per minute of patient-serum samples to counts per minute of control-serum samples. Normal values are less than 2.0. All assays were done in triplicate.

Serum Drug-Dependent Antiplatelet IgG. The method was that described for serum antiplatelet IgG, except that serial dilutions of serum from 1:2 to 1:64 were mixed with 1 mM final concentration of drug being tested.

The drugs tested were those most likely to have caused the patient's thrombocytopenia by clinical time course criteria: diltiazem, diazepam, isosorbide dinitrate, quinidine, heparin, morphine. Tests were run concurrently with a control of serum plus no drug. Assays were conducted using the same lots of drug from which the patient's dose had been taken, except for the assays of morphine and heparin. Samples of serum drawn on hospital day 17 and at 5 months after discharge were assayed. Results were expressed as mean ratios of counts per minute of patient serum to control serum. A ratio greater than 1.3 was considered a positive result. All assays were performed in triplicate.

The purpose of this test was to obtain in vitro evidence that one of the drugs caused the patient's thrombocytopenia.

Results

Peripheral smear showed decreased platelet count with increased size and normal red- and

TABLE
Results of Drug-Dependent Serum Antiplatelet Antibody Assays

Dilution of drug	No drug	Diltiazem	Diazepam	Isosorbide-dinitrate	Quinidine	Heparin	Morphine
Day 17							
1:2	–	+	–	–	–	–	–
1:4	–	+	–	–	–	–	–
1:8	–	–	–	–	–	–	–
1:16	–	–	–	–	–	–	–
1:32	–	–	–	–	–	+	ND
1:64	–	–	+	–	–	+	ND
5 months postdischarge							
1:2	–	–	–	–	–	–	–
1:4	–	–	–	–	–	–	–
1:8	–	–	–	–	–	–	–
1:16	–	–	–	–	–	–	–
1:32	–	–	–	–	–	ND	ND
1:64	–	–	+	–	–	ND	ND

Positive (+): mean ratio of counts per minute, patient serum to control serum, greater than 1.3.
ND, not done.

white-cell morphology and counts. Bone marrow aspirate showed increased megakaryocyte number and size. Therefore, both smear and marrow were consistent with peripheral platelet destruction rather than marrow suppression. There was normal erythrocyte and granulocyte maturation.

Platelet-Associated IgG. Results of this assay suggested an immune rather than direct toxic etiology of platelet destruction.

Assay of antiplatelet IgG showed increased values in samples from day 17 and 4 months after discharge (7.6 ng/10^7 platelets and 13.1 ng/10^7 platelets, respectively—normal = 2.81 ± 1.2 ng/10^7 platelets). Antiplatelet IgG had decreased to the normal range (3.0 ng/10^7 platelets) by 5 months after discharge.

Serum Antiplatelet IgG. Serum antiplatelet IgG was normal at serum dilutions of 1:2–1:16. Results ranged from 0.95 to 1.59. Normal values are less than 2.0.

Serum Drug-Dependent Antiplatelet IgG. A screening assay of the most likely drugs (diltiazem, diazepam, isosorbide dinitrate, and quinidine) was performed at a serum dilution of 1:2 using serum drawn on hospital day 17. Diltiazem, diazepam, and isosorbide dinitrate were positive for drug-dependent antiplatelet antibodies at this high concentration. The assay was then repeated at dilutions of 1:2–1:64 for the same four drugs as well as morphine and heparin. Serum samples taken on hospital day 17 and 5 months after discharge were assayed. Results are summarized in the Table.

Discussion

Causes of thrombocytopenia can be broken down into three broad categories: (a) decreased production, (b) increased sequestration, and (c) increased destruction of platelets. Drug-induced thrombocytopenia belongs to either the first category, as from a direct toxic effect on the bone marrow (of chemotherapy, for example), or the third category. Causes of drug-induced peripheral destruction of platelets are either immune or nonimmune. An example of nonimmune destruction is enhanced platelet aggregation seen with ristocetin. Immune drug-induced thrombocytopenia has been associated with a number of drugs (3), most notably quinidine. The diagnosis of immune drug-induced thrombocytopenia is one that requires excluding nonimmune thrombocytopenia, as well as proving that the thrombocytopenia has an immune basis.

An important first step in the differential diagnosis is examination of the peripheral smear and bone marrow aspirate. In cases of increased platelet destruction, the platelet count decreases and megathrombocytes are seen in the smear. Red and white cells are normal. Bone marrow shows increased megakaryocytes, with normal maturation of erythrocyte and granulocyte series. The patient described met these criteria.

If drug-induced immune thrombocytopenia is suspected clinically after these tests, Hackett et al (4) outline four criteria to be used in the diagnosis of immune drug-induced thrombocytopenia and require that criteria 1, 2, and 3 or 1, 2, and 4 be fulfilled for the diagnosis of drug-induced immune thrombocytopenia. This patient met criteria 1, 2, and 4, the argument being as follows.

Criterion 1. The first criterion is that the clinical history must be consistent with the drug in question having caused the thrombocytopenia. Specifically, thrombocytopenia must develop during treatment with the drug, resolve with its discontinuation, and must not recur while the patient is off the drug. Typically, the patient has a history of previous exposure to the drug, although it is possible for immune thrombocytopenia to develop on prolonged exposure to the drug the first time it is given. After a period of days of treatment, the platelet count drops precipitously, sometimes resulting in purpura or hemorrhagic phenomena. When the drug is withdrawn, the platelet count recovers within approximately one week.

The patient described fits the first criterion. The drugs introduced early in the patient's course and therefore most likely by clinical history to have caused thrombocytopenia were diazepam, quinidine, diltiazem, and morphine. Within one week after these drugs were withdrawn, the platelet count began to normalize, consistent with one of them having caused the thrombocytopenia. Isorbine dinitrate (Isordil) or other intravenous nitrates and morphine were used throughout his course, so these drugs were considered unlikely on a historical basis. This left diltiazem, quinidine, and diazepam as the most likely drugs, to be further tested by in vitro assay.

Criterion 2. The second criterion is that other immune and nonimmune causes of thrombocytopenia must be excluded by history and physical and laboratory examination. The patient described had no collagen vascular disease, neoplasm, splenomegaly, or infectious process and was exposed to no causative agents other than the ones noted in the clinical description. Since he had no other intrinsic or extrinsic cause for thrombocytopenia, he met the second criterion.

Criterion 3. The third criterion is that thrombocytopenia should recur when the patient is rechallenged with the drug. Although this is the definitive test, it is a considerable risk to the patient and is unacceptable unless there is no drug that can be used in its place. If this is the case, restarting use of the drug must be closely supervised. In this case, the medical team was faced with this dilemma: the patient needed chronic antiarrhythmic therapy and previous agents had failed, so quinidine use was restarted on day 40 and the patient was closely watched. His platelets stayed stable, an outcome that excluded quinidine as a cause. Heparin therapy began late in his hospital course and did not affect platelet recovery, ruling out heparin as a cause of immune thrombocytopenia.

Of the remaining likely drugs (diazepam and diltiazem), only diazepam has been described in the past as having satisfied Hackett's criteria for drug-induced thrombocytopenia (5). Diltiazem has never been previously described as having this side effect.

Criterion 4. The fourth criterion is a positive in vitro test of immune platelet destruction. These assays are described in several places (5–12). The tests used in this patient's case measured platelet-associated IgG (which was elevated, consistent with an immune mechanism), serum antiplatelet antibodies, which are elevated in 40% of immune thrombocytopenia (13), and drug-dependent serum antiplatelet antibodies. The last test is the most relevant here, since it should reveal the drug responsible for the immune thrombocytopenia (12). In the assay, patient serum plus drug causes increased binding of IgG to normal platelets.

The in vitro assays in this patient supported both diltiazem and diazepam as causes of the thrombocytopenia, and excluded morphine (Table). Elevated antiplatelet IgG supported an immune cause of decreased platelets. The lack of serum antiplatelet IgG did not exclude a drug-induced cause, since a negative result may reflect the need for drug presence for a drug-antibody complex to bind to the platelet, or for the drug to bind to the platelet before the antibody binds to the drug. The specific drug studies supported diltiazem (positive at 1:2 and 1:4 dilutions on day 17) and diazepam (positive at 1:64 dilution on day 17 and 5 months after discharge). Heparin was also positive on day 17 at 1:32 and 1:64, but had been ruled out on a historical basis. Diazepam was considered an unlikely cause of the patient's thrombocytopenia historically, given his many previous years of exposure to Valium with no adverse effects. However, the fact that more than one drug was positive suggests one of three possibilities: that the assay is not as specific as previously stated (12); that this particular patient was likely to develop multiple drug sensitivities (suggested by a lupuslike reaction to a trial of Pronestyl during this hospitalization); or that more than one drug interacted to produce the thrombocytopenia.

On the basis of the above data, diltiazem fulfilled Hackett's criteria 1, 2, and 4 and was therefore the most likely cause of the patient's thrombocytopenia. Other possible causative drugs were excluded, as discussed. These findings should alert clinicians to the possibility of diltiazem-induced thrombocytopenia in their own patients.

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Psychological ACTH Dependency: Case Report and Review of the Literature

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Abstract

Reported here is the case of a 33-year-old white woman who became addicted to daily ACTH injections used in conjunction with corticosteroids. After 27 months of dependence on ACTH injections, intensive medical and psychiatric treatment helped her to discontinue the habit. In-depth review of the literature disclosed that addiction to ACTH injections has been reported only twice before. The hypothesis is that ACTH and endorphin contained in the ACTH preparation may play a role in perpetrating dependency on ACTH injections. Owing to the wide availability of injectable ACTH, further studies are needed to clarify the addictive potential.

Case Report. A 33-year-old white woman, a teacher, had a history of nausea, weight loss, lack of energy, myalgia, and headaches. The patient's mother had committed suicide using an overdose of an unspecified medication, and her father had been under psychiatric care for mental depression. The patient was very anxious and denied taking any medication. On physical examination the patient weighed 125 lb; blood pressure was 120/80 mm Hg without orthostatic changes, and pulse was 80/min. The only other major finding was mild acne on her face. Laboratory results were also normal.

ACTH test showed a blunted rise in plasma cortisol and no response in urinary 17-hydroxysteroids (Table). Metyrapone test showed a paradoxical decrease in urinary 17-hydroxysteroids (urinary 17-hydroxysteroids were 9.3 mg/day before metyrapone administration and decreased to 4.1 mg/day after administration of 750 mg of metyrapone by mouth for six doses). These tests confirmed the diagnosis of adrenal insufficiency (1). Because of the symptoms and the laboratory test results, treatment was started with 30 mg hydrocortisone administered daily. For the following 7 months the patient was maintained on oral steroid therapy. She insisted on taking a variety of steroid medications (dexamethasone, hydrocortisone, and cortisone acetate). Her preoccupation with various medications resulted in the additional intake of nonsteroidal medications such as Atarax, Dexedrine, Ionamin, bellergal, and hydrochlorothiazide. At this point, physical examination showed no changes. She did not keep several appointments, and when seen four months later, she was injecting herself with ACTH (40 units every other day) and taking oral celestone, 0.6 mg daily, both prescribed by another physician.

Over the following 16 months, repeated attempts to discontinue or lower the ACTH dose were unsuccessful, and she developed cushingoid features with excessive weight, moonface, skin striae, and hypertension, due to self-induced overindulgence in ACTH injections. At this time, a combined medical and psychiatric effort was made to wean her of steroids. The patient was hospitalized and received placebo injections with normal saline, but she became irritable, restless, and weak and complained of myalgia. She also developed objective signs of withdrawal: pupillary dilatation, diaphoresis, and tachycardia. She requested the injections and demanded to be discharged "to take her ACTH injections at home." She was discharged, and on various occasions she

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TABLE
Results of ACTH Test

Time (hr)	ACTH (IU)*	Cortisol (μg/dl)†
0	25 IV	2.0
1	80 IM	6.4
7		11.6

Concomitant urinary 17-hydroxysteroids: 1.6 mg/day.
* Administered ACTH.
† Plasma cortisol.

stated that she "needs ACTH like a diabetic needs insulin" and that abstaining from ACTH caused limb paresthesias, depression, and weakness. From this time on, it became clear that the patient was addicted to and dependent on ACTH. In spite of hypertension, she claimed that measurements with her own sphygmomanometer at home showed blood pressure in the normal range. She went to a hypnotist in an attempt to lose weight. Following an intense medical-psychiatric effort and a combined diet and exercise program, she was weaned of steroids completely and lost the 30 lb that she had previously gained while on steroids; her blood pressure normalized after 27 months of ACTH dependence.

Discussion. This patient presents several clinical problems, one of which is diagnostic. From the first visit it was apparent that she had clinical and laboratory evidence of hypothalamic-pituitary-adrenal axis suppression, proved by three cortisol levels below 15 mg% following one injection of 25 units of ACTH intravenously and another of 80 units intramuscularly (1). This diagnosis was supported by very low urinary 17-hydroxysteroids and a paradoxic metyrapone test. However, previous ingestion of steroids might have produced spuriously abnormal results. Not satisfied with the standard treatment of adrenal insufficiency with oral steroids, the patient sought and received ACTH injections, to which she became habituated. As a result, another clinical problem emerged—drug dependence. In spite of repeated advice against the use of ACTH, the patient felt dependent on this drug, and persistent attempts to discontinue or reduce the dose failed.

Review of the English-language medical literature disclosed a similar case of a 40-year-old physician, alcoholic for seven years, who took large amounts of psychotropic drugs, propylthiouracil, and Dexedrine (2) who became dependent on injections of ACTH and used them for three consecutive years. As did the patient described here, he developed cushingoid features, hypertension, and skin bruises. Two other cases have been reported, in a one-year study of 156 patients with multiple sclerosis who were receiving 15–25 units of ACTH daily; when treatment ceased, two patients insisted on continuing the drug (3).

ACTH may be involved in the etiology of morphine addiction. According to Jacquet (4), there are two receptors for morphine: an endorphin-stereospecific receptor blocked by naloxone, and a naloxone-insensitive, nonstereospecific receptor mediating narcotic dependence, whose ligant may be endogenous ACTH. In this study, injection of ACTH into the periaqueductal gray matter of drug-naive rats produced a withdrawal syndrome similar to that elicited by morphine withdrawal. This syndrome was blocked when the rats received previous intraperitoneal injections of morphine. Rats that received morphine in the periaqueductal gray matter developed both effects, namely, analgesia and hyperactivity.

Further evidence of the possible synergism between ACTH and morphine has been accumulated through ablation experiments. Hypophysectomy, a maneuver that decreases endogenous ACTH levels, enhances the development of tolerance to opiates (5). This increased tolerance is reversible by ACTH administration. It is significant that adrenalectomy, known to increase plasma ACTH levels, increases morphine uptake into the brain and enhances morphine analgesia (6). Moreover, in rats, dexamethasone administration, known to decrease plasma ACTH levels, decreases electroacupuncture anesthesia (7).

Of interest is the fact that injectable corticotropin (manufactured by Armour) contains 65 guinea pig units (GPU)/mg of endorphin (8), resulting in an endorphin:ACTH ratio of 2.6. Beta-endorphin is an endogenous morphinelike polypeptide that is found in the pituitary gland, stored in the same cells that contain ACTH, and released in conjunction with ACTH into the blood (9). Its release can be blocked with steroids and stimulated with metyrapone (10). Some of the effects of endorphin in rats are similar to those of morphine and can be blocked by the morphine antagonist nalorphin. Endorphin dependence is another possible explanation for ACTH addiction in the four patients described, and further studies to clarify this intriguing link are needed.

Since injectable ACTH is useful as a test for adrenal insufficiency and is occasionally prescribed for treatment of various conditions, it is important to recognize the possible complication of drug habituation to ACTH.

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Superior Vena Cava Syndrome Due to Mucormycosis in a Patient with Lymphoma

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Abstract

A patient is presented who developed the superior vena cava syndrome during treatment of diffuse lymphocytic lymphoma. He had a progressively downhill course and died despite treatment with broad-spectrum antibiotics and mediastinal radiotherapy. At postmortem examination the superior vena cava and several other large vessels were found to be filled with thrombi containing fungal organisms compatible with a species of Mucoraceae. The association of fungal sepsis and the superior vena cava syndrome is discussed.

Opportunistic infection is an ever-present threat to the patient who is leukopenic during treatment of hematologic malignancy. Bacterial infections may be treated presumptively with broad-spectrum antibiotics; because of the toxicity of antifungal agents, fungal infections usually require specific diagnosis prior to treatment. Because fungi are difficult to grow from blood or secretions, diagnosis frequently requires invasive procedures (1). Knowledge of disease patterns and a high index of suspicion are therefore essential if cure is to be effected.

We present a patient who developed the superior vena cava syndrome during treatment of lymphoma. He was treated with radiotherapy for presumed malignant compression of the cava. At autopsy the superior vena cava was thrombosed with fungal hyphae characteristic of Mucoraceae. Absence of a peripheral site for biopsy or culture made this a particularly difficult case to diagnose. Whereas the superior vena caval syndrome is rarely due to thrombosis associated with fungal infection, intravascular localization is typical of mucormycosis. This case teaches that fungal infection should be considered in the differential diagnosis of large blood vessel obstruction in patients susceptible to opportunistic organisms.

Case Report

The patient was a 62-year-old white man undergoing treatment for diffuse, poorly differentiated lymphocytic lymphoma who was admitted to The Mount Sinai Hospital because of leukopenia.

The patient was well until 1980, when he developed axillary adenopathy. Lymph node biopsy in March 1981 performed at another institution was interpreted as diffuse, well-differentiated lymphocytic lymphoma. At that time clinical staging revealed involvement of abdominal, mediastinal, and inguinal nodes as well as the spleen. Bone marrow biopsy was negative. The patient was treated with chlorambucil until May 1982, when his adenopathy began to increase. In September 1982, he was started on cyclophosphamide, vincristine, and prednisone. Adenopathy recurred in May 1983, and by October bone marrow biopsy showed infiltration with malignant cells. He was treated with cyclophosphamide, Adriamycin, vincristine, and prednisone until March 1984, when an axillary node biopsy was interpreted as diffuse, poorly differentiated

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lymphocytic lymphoma. In April and May he was treated with Adriamycin, cisplatin, and etoposide, and in June he was treated with mitaxantrene, vincristine, and dexamethasone. In response to the last treatment the spleen and lymph nodes decreased in size. The white blood cell count fell to 200/mm^3, and he was admitted for observation.

On admission, the patient was afebrile and in no distress. He had a 4.0 × 3.0 cm mass on the left side of the neck. The liver edge was palpated two fingerbreadths below the right costal margin, and the spleen tip was palpable. The hemoglobin value was 11.4 gm, white blood cell count 200/mm^3, platelet count 64,000/mm^3, BUN 31 mg%, creatinine 1.3 mg%, bilirubin 0.8 mg%, SGPT 193 mg%, and SGOT 71 mg%. Chest x-ray showed hilar adenopathy and a wide superior mediastinum.

The hospital course was characterized by spiking temperatures despite the administration of multiple broad-spectrum antibiotics, including cefazolin, tobramycin, mezlocillin, amikacin, piperacillin, 5-flurocytocine, and acyclovir. Miconazole was given for only one day owing to development of a rash. Amphotericin B was originally withheld because of a previously documented hypersensitivity. Cultures showed only *Candida albicans* in the throat and toxin-negative *Clostridia difficile* in the stool. Rhizopus species was isolated from sputum three days prior to death.

Five days after admission the patient noticed jaundice. His bilirubin was 6.1 mg% and it persisted in the 6–10 mg% range for the rest of the course. Three days later and eight days prior to death he complained of hoarseness and was noted to wheeze after miconazole administration. Chest x-ray showed a mass in the right suprahilar region (Fig. 1). Shortness of breath became a more persistent problem and facial edema was noted. Five days prior to death, radiotherapy was begun for presumed malignant superior vena cava syndrome. Respiratory distress persisted and he became lethargic. He was intubated and given 71 mg of amphotericin B prior to death. He remained febrile, however, and became obtunded. He died three days after intubation.

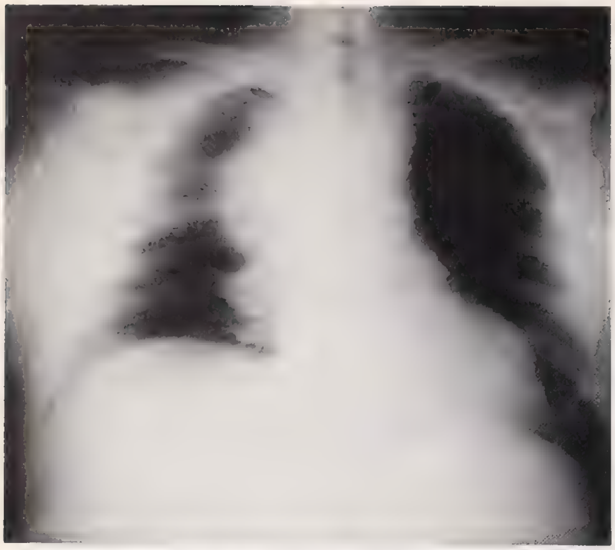
Autopsy Findings. At autopsy, the body was mildly jaundiced and there was gross edema of the head and neck. The thoracic cavity contained 500 cc of serosanguinous fluid in the right pleural space and 100 cc in the left. The spleen was enlarged to 6 cm beneath the left costal margin.

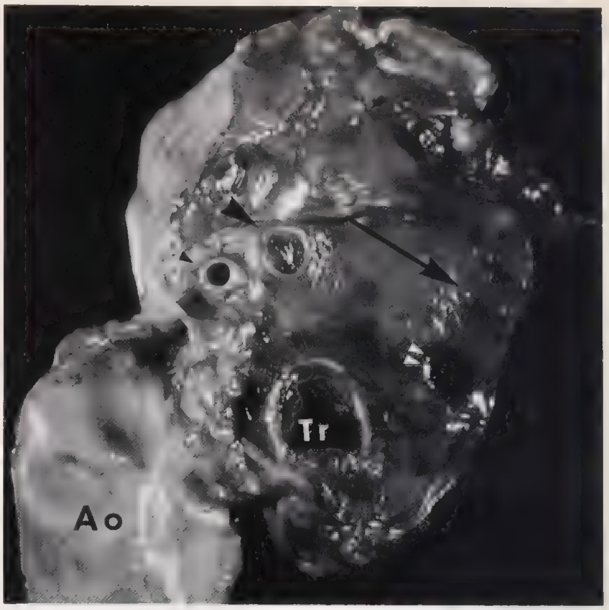
There was a 14.0 × 12.0 × 11.0 cm mass in the mediastinum with its lower border located just above the takeoff of the pulmonary artery and aorta. It lay to the right of the mediastinum and was distinct from the right lung. The right upper lobe was uniformly firm and hemorrhagic. The right upper lobe pulmonary artery and peripheral radicals and the proximal pulmonary veins were occluded by thrombus. The superior vena cava was occluded up to the bifurcation of the right innominate vein. Thrombus extended into the internal jugular and subclavian veins. Only partial occlusion of the left innominate vein was found. The innominate artery was entirely occluded with thrombus, which extended 3.0 cm into the right common carotid artery and 1.5 cm into the right subclavian artery (Fig. 2). At its proximal end the thrombus extended into the aorta, obstructing 80% of its lumen. Microscopic examination of the thrombi revealed broad, nonseptate fungal hyphae with 90° branching compatible with Mucoraceae (Fig. 3).

In addition to thrombosed vessels, the mediastinum contained remnants of normal lymphoid tissue and numerous hyphal elements. No tumor could be identified. The right upper lobe was hemorrhagic and showed hyphae in the parenchyma as well as in blood vessels. The myocardium showed small, ill-defined white foci, 0.2–0.5 cm in diameter, which on microscopic examination revealed foci of necrosis and fungal hyphae. The spleen and liver had one infarct each. Microscopically, hyphae diffusely infiltrated the parenchyma as well as the vessels supplying the infarcted areas. Fungal hyphae were also found in the kidneys and in the paraaortic lymph nodes. The bone marrow was hypocellular and contained paratrabecular aggregates of atypical lymphocytes. These represented residual foci of lymphoma.

Discussion

Superior vena cava syndrome is not an uncommon complication of cancer involving the mediastinum. Conversely, the majority of all cases of the superior vena cava syndrome are due to malignancy. In a recent series from the Mayo Clinic, 78% of the 86 cases seen between 1960 and 1979 were due to malignant compression of the vessel. Eight (8.4% of the malignancies) were lymphomas (2). In the setting of previously documented malignancy in the chest it is common practice to begin radiotherapy without repeated tissue documentation (3). Our patient was presumed to have malignant compression of the cava despite the suspicion of concurrent infection.





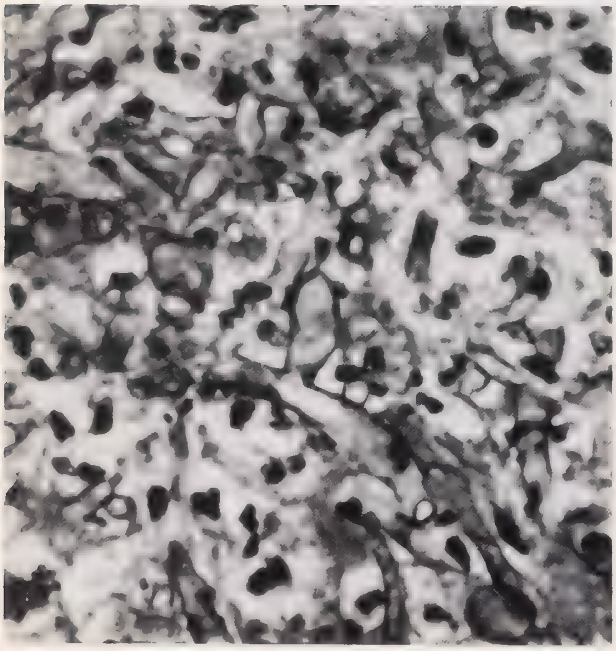


Fig. 1. Above left Chest x-ray obtained 8 days prior to death showing right suprahilar mass. **Fig. 2. Above right** Transverse section through mediastinum. Superior vena cava (arrow) and innominate artery (arrowhead) are both occluded by fungal thrombus. Left common carotid artery (small arrowhead) and a lymph node (double small arrowheads) are also indicated. Ao, aorta; Tr, trachea. **Fig. 3. Left** Mediastinal thrombus, showing broad, nonseptate hyphae with 90° branching (PAS, original magnification ×400).

In recent years, intensive chemotherapy has changed the natural history of some malignancies. Many patients with lymphoma and leukemia may expect prolonged survival; death is as likely to be due to infection as to disseminated tumor (4). Despite this increased incidence of opportunistic infection, superior vena cava syndrome caused by fungal thrombosis remains a rare clinical entity. In the series from the Mayo Clinic, 19 patients had benign etiologies, but none of them had active fungal infection (2). Similarly, in a series of 16 patients with benign superior vena cava obstruction reported from the Cleveland Clinic, none had fungal infection (5). There are two case reports of this entity. Both patients had acute myelogenous leukemia and were undergoing intensive chemotherapy. Both developed signs of pneumonia and terminally the superior vena cava syndrome. In each case the correct diagnosis was made only at autopsy; one patient had infection with *Aspergillus* (6) and the other with *Mucor* (7).

Rhizopus, a fungus of the family Mucoraceae, was isolated from the sputum of our patient antemortem. This organism is one of the common bread molds and meat spoilers. Although it is ubiquitous and grows easily (8) on standard laboratory media, it is not a common laboratory contaminant. In tissue it is recognized by its broad, nonseptate hyphae with 90° branching. Because of its large size and staining characteristics it is easily seen on routine hematoxylin and eosin preparations as well as with special stains (9).

The Mucoraceae share with *Aspergillus* the propensity for invading blood vessels. Pathologically the typical lesion includes vascular channels filled with organisms and infarction of the subtended tissue. The inflammatory response is characteristically mild, especially in leukopenic patients (10, 11). The difficulty in making the diagnosis may relate to the intravascular localization of the organism and the lack of inflammatory exudation. As in our case, very large vessels may be involved. Main pulmonary arteries are frequently thrombosed, as are the carotid arteries (10). There is a case report of renal vein thrombosis and one of complete hepatic artery thrombosis (1). The other case of superior vena cava obstruction was mentioned earlier.

Infection with Mucoraceae occurs most commonly in diabetics and in immunosuppression patients. Diabetics are particularly susceptible to localized rhinocerebral disease. Disseminated infection is more common in patients with hematogenous malignancy than in patients with solid tumors, and it is highly associated with periods of leukopenia (12). The most common portal of entry is the upper airway, and pneumonia is the most common clinical presentation. During dissemination, the brain, kidneys, and spleen are sites of localization (1).

Despite the absence of symptomatology, our patient's infection probably originated in the respiratory tract. A small focus of fungal growth in a peripheral lung unit may have gained access to the vascular tree and reached the hilum by retrograde extension through the pulmonary arteries. From the hilum there may have been contiguous spread to the mediastinum and great vessels. Because of the early vascular localization, signs of pneumonia appeared only with terminal dissemination. In addition, the pulmonary veins were much less involved than were the pulmonary arteries. It was probably not until the veins were occluded that bronchial artery flow was disrupted and pulmonary infarction ensued.

In summary, we have presented a patient with lymphocytic lymphoma who developed disseminated mucormycosis associated with superior vena cava syndrome. The patient was typical of those who develop mucormycosis, but the late development of the pulmonary infiltrate delayed the diagnostic workup. We realize that this patient is unusual, but it is important to emphasize that the superior vena cava syndrome may be caused by an infectious agent even in the setting of malignancy. This is especially true for patients with leukemia or lymphoma, who seem to be particularly prone to mucormycosis and aspergillosis.

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Massive Intraabdominal Bleeding in Polyarteritis Nodosa

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Abstract

Spontaneous retroperitoneal hemorrhage is a rare and catastrophic complication of polyarteritis nodosa (PAN). Less than 40 cases of life-threatening bleeding caused by PAN have been reported, survival ranging from one day to three years. The case of a 30-year-old man with PAN who developed massive retroperitoneal hemorrhage is described. Provided an early diagnosis can be made, a conservative approach is to be preferred, although surgical exploration is often unavoidable. The use of MAST trousers, a therapeutic modality as yet undescribed for this entity, is advocated to stabilize the actively bleeding patient while appropriate diagnostic or therapeutic arteriography is performed. This modality may also be used to control recurrent hemorrhage and thus avoid unnecessary surgical exploration.

Spontaneous retroperitoneal hemorrhage, a rare and catastrophic complication of periarteritis nodosa, is caused by rupture of microaneurysms often found in the kidney. Prior to the use of selective arteriographic studies, this condition was rarely diagnosed prior to surgery, and nephrectomy was the treatment of choice. Emphasis should be placed on avoiding surgery altogether, although this is usually not possible. Our experience has shown that, in addition to radiographic studies and vigorous medical treatment, MAST trousers can be of great value both to stabilize the actively bleeding patient and to control recurrent hemorrhage.

Case Report

A 30-year-old man came to the emergency room after being awakened by sudden excruciating left-upper-quadrant pain that radiated to his left shoulder. He had been hospitalized two months earlier with polyarthralgias and hypertension, for which he was treated with aspirin and clonidine. His medical history was otherwise negative. On physical examination the patient was anxious and in acute distress. He was severely orthostatic, with blood pressure of 180/110 mm Hg in the supine position and 110 mm Hg in the upright position. His pulse was 120 and regular. The abdomen was distended, and a large, tender, diffuse mass was palpable in the left upper quadrant. No organomegaly was noted. Bowel sounds were normoactive. There was no joint tenderness or swelling, and no lymphadenopathy.

Laboratory results included a hematocrit of 37% and a white blood cell count of 27,000 without a left shift. Electrolytes were normal. The amylase was 85 and the erythrocyte sedimentation rate (ESR) 120. Urinalysis showed microhematuria. The patient was not acidotic. The prothrombin time was normal. The chest x-ray was normal. A flat plate of the abdomen revealed a medially displaced splenic flexure. The nasogastric aspirate and stool were negative for occult blood.

After the patient received 2,600 cc of intrave-

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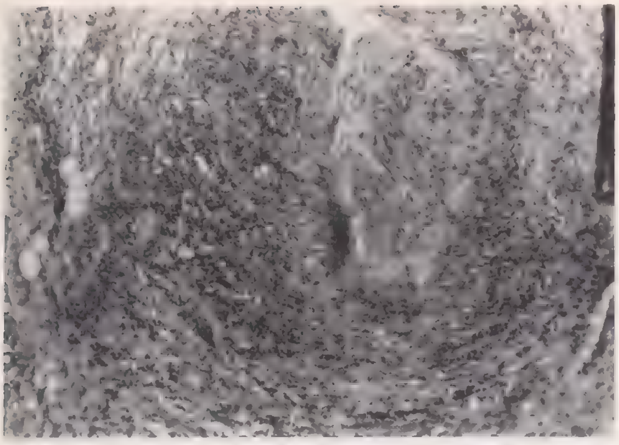


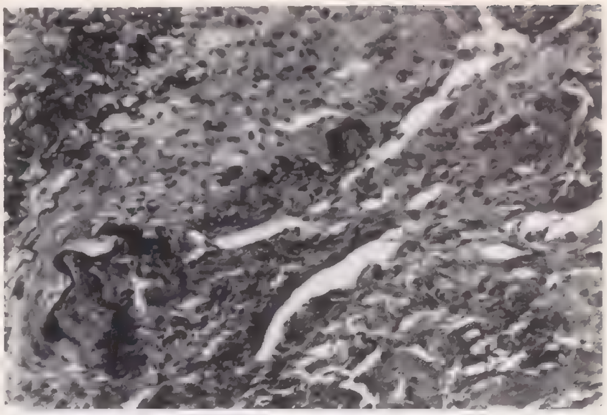


Fig. 1. **Left** Pathologic specimens showing thrombosed artery in periadrenal fat with severe inflammation and destruction of intima and media. Fig. 2. **Right** Destruction and fragmentation of arterial elastica from previous necrosis.

nous fluids, his hematocrit dropped to 26%. Abdominal paracentesis was grossly clear, and the red blood cell count after lavage was only 7,300/mm^3. The hematocrit was unchanged in spite of blood transfusion of two units. An exploratory laparotomy was performed.

When the abdominal cavity was examined, a large hematoma was found in the left retroperitoneal compartment extending from the iliac crest to the diaphragm. The gallbladder was full of stones, but there was no inflammation. The aorta was controlled at the hiatus, and the left colon and splenic flexure were mobilized. Approximately 2 L of blood and clots was evacuated from the left perirenal area. No active bleeding was observed. The left adrenal vein and other small retroperitoneal vessels were suture-ligated. A large sump drain was left in place anterior to the kidney prior to closure.

Postoperatively the patient became hypotensive, oliguric, and agitated, and was reexplored. Three liters of clot and blood was evacuated from the operative field. Bleeding was observed from a small arterial vessel on the surface of the kidney and was controlled by oversewing the parenchyma with large figure-of-eight chromic sutures. The spleen and left adrenal were removed to facilitate hemostasis.

In the postoperative period the patient remained hemodynamically stable, requiring only Aldomet for his hypertension. Aside from a transient episode of respiratory insufficiency requiring assisted ventilation, the patient recovered well. Further laboratory data showed an ESR of 111 and a positive antinuclear antibody. The anti-DNA antibody, latex fixation test, and C3, C4, and serum protein electrophoresis were all normal.

Pathologic examination of the spleen and adrenal gland showed polyarteritis nodosa in both active and healing stages (Figs. 1, 2). The patient did well until the eleventh postoperative day, when he suddenly went into shock. Resuscitation measures included large volumes of intravenous fluids and blood. MAST trousers were applied to attempt to tamponade the bleeding. The patient's condition promptly improved and his vital signs stabilized. An emergency angiogram showed no active bleeding but revealed multiple aneurysms in the left kidney, mesocolon, and liver (Figs. 3, 4). The patient was placed on a regimen of antihypertensives, high-dose prednisone, and cytoxan, which he tolerated well. His ESR fell to 20. Eighteen months later, although symptom-free from the PAN, he developed acute cholecystitis. He underwent uneventful cholecystectomy and recovered without complication.

Discussion

Periateritis nodosa is a well-known necrotizing vasculitis of small and medium-size arteries. This systemic disease may affect any organ system, but renal involvement is a constant finding in 80% of cases. Two-thirds of these patients develop chronic renal failure and hypertension as a result of both glomerular and interstitial changes. The prognosis is poor, especially with the onset of hypertension; life expectancy is reduced to less than one year if untreated (1). Few cases of complete remission with high-dose steroids, immunosuppression, and antihypertensives have been reported (2–5).

Patients with intraparenchymal renal aneurysms are at high risk of developing spontaneous retroperitoneal hemorrhage, especially if they are hypertensive. This catastrophic complication of PAN is rare; less than 40 cases are described in

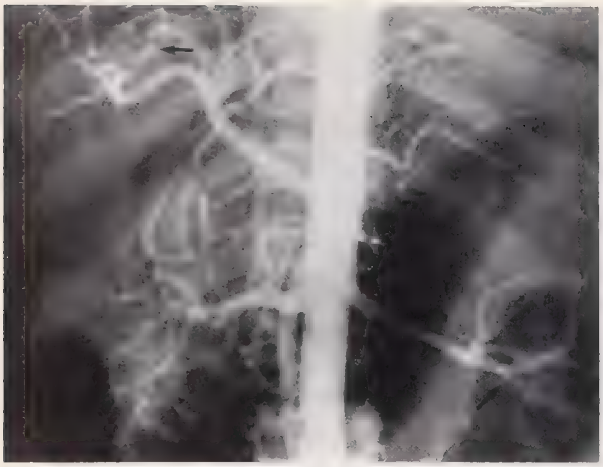
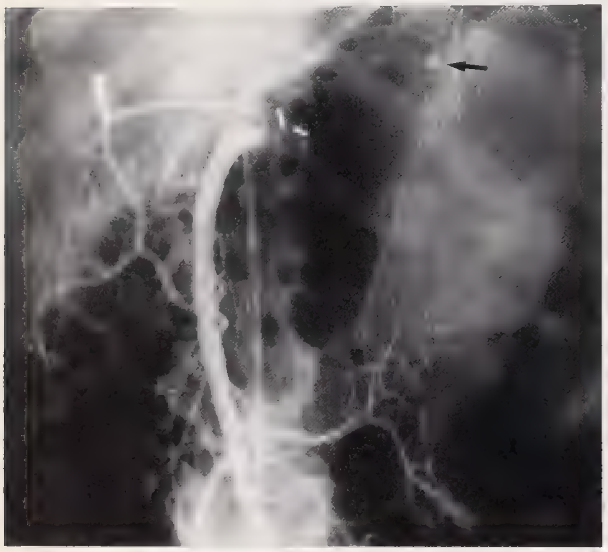


Fig. 3. Above Flush aortogram showing small aneurysms in left kidney and liver (arrows). **Fig. 4. Below** Selective superior mesenteric arteriogram showing intramesenteric aneurysm (arrow).



the literature. Vasculitides in general are the second leading cause of spontaneous perirenal hemorrhage, but PAN is the specific diagnosis in only 10% of these (6, 7).

The clinical presentation of PAN is often confusing, since symptoms, signs, and laboratory data are nonspecific. The diagnosis is primarily radiologic, and confirmation is obtained on reviewing a pathologic specimen.

In the emergency situation, a high index of suspicion based on history alone should alert the clinician to obtain an emergency angiographic study. Aneurysms can be demonstrated angiographically in the parenchyma of the kidneys, spleen, liver, and other organs, as well as in the mesenteric vessels. Only a small percentage of patients with PAN are found to have aneurysms, but when demonstrated, they are pathognomonic (4), and once there is development of systemic hypertension, rupture occurs in more than 50% of cases (8). Interestingly, prior to the routine use of angiographic studies, the diagnosis of PAN in patients with spontaneous hemorrhage was made only at postmortem examination (9). Selective mesenteric or renal studies have been invaluable (4, 5, 10–12) and can allow for embolization in the face of active bleeding.

The pathophysiologic process involved in PAN is the focal deposit of immune complexes that results in an inflammatory reaction with eventual fibrinoid degeneration of the vessel wall. The healing stage is characterized by fibrosis, nodular thickening, and aneurysmal dilations. Polymorphic lesions representing all stages of the degenerative phase and healing process can be demonstrated histologically within the same vessel. Aneurysm formation is rarely demonstrable in normotensive patients, but is not uncommon in hypertensive patients with proven PAN (13). The combination of hypertension and weakening of the arterial wall is the basis for the spontaneous hemorrhage described. Of 32 reported patients with PAN complicated by spontaneous retroperitoneal hemorrhage, 20 were hypertensive (1–5, 9, 10, 12, 14).

Management. Management of this particular entity presents a difficult clinical problem. One is faced with a patient in extremis with no history of trauma, and with massive intraabdominal bleeding. Once the more common causes of abdominal apoplexy, such as spontaneous splenic rupture or rupture of an abdominal aortic aneurysm, are ruled out, one is left with a diagnostic dilemma in the context of a life-threatening situation.

Vigorous supportive treatment is mandatory. If intravenous fluids and transfusions do not adequately stabilize the patient, MAST trousers can be applied to allow time for emergency angiography. Once this is performed and a bleeding point is located, a directed surgical exploration can be undertaken, or intraarterial embolization attempted.

In the face of a systemic disease such as PAN, in which bilateral renal involvement must be anticipated, most authors agree that preservation of as much functional parenchyma as possible is mandatory (8, 10, 12, 15). Unfortunately, the literature is clouded by reports that show a high mortality for both nonoperative (100%) and conservative surgical (50%) approaches, as contrasted with a relatively low mortality with nephrectomy (20%) (6, 7). There has even been a case in which bilateral nephrectomy was performed (15). It must be pointed out that these reports take into consideration perirenal hemorrhage of all etiologies, and none of the cases had the benefit of preopertive arteriography.

Once the diagnosis of PAN is established either clinically or with pathologic specimen, vigorous immunosuppressive treatment with high-dose steroids and cytoxan must be started and the hypertension brought under control. This is important because the bleeding tends to be recurrent, as seen in our case and in others (12). With an appropriate medical regimen, repeat arteriographic studies have demonstrated a significant reduction in both the number and size of the aneurysms (4). The only other reported long-term survivor was in fact treated with angiographically guided selective surgical repair followed by appropriate immunosuppressive and antihypertensive therapy (3).

There are several important points in the case presented. Although on initial clinical examination the patient was in severe hemorrhagic shock, at exploration there was no true discernible point of bleeding, even though the patient's systemic pressure had been restored. The patient then suffered two recurrent episodes of life-threatening hemorrhage. This is typical of these cases and belies the fact that PAN is a systemic disease that causes diffuse aneurysm formation.

Also noteworthy is that the final bleeding episode was controlled successfully with MAST trousers, allowing for prompt arteriography and institution of immunosuppressive medications that had been withheld during the initial postoperative period. MAST trousers are routinely used in emergency departments for trauma victims and for patients with ruptured abdominal aortic aneurysms to allow time to stabilize the patient while maintaining adequate perfusion pressures prior to surgery. Their use in this setting has not previously been described.

Retrospectively, the MAST trousers might have been useful in this case to control the initial bleeding episode. Arteriography would then not have been delayed, and there would have been time to plan a more directed surgical approach. One can speculate whether surgery could have been avoided altogether had the bleeding been controlled. It should be emphasized that prompt diagnosis allows immediate, specific medical treatment, which is essential because it is the only common denominator found in long-term survivors.

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Avascular Necrosis of the Femoral Head In Patients Being Treated for Malignancy

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Abstract

When a patient being treated for cancer develops hip pain, the diagnosis of metastases to the region must be differentiated from avascular necrosis of the femoral head. In the years 1970–1983, 12 patients at The Mount Sinai Medical Center in New York City developed avascular necrosis (AVN) of the femoral head during or after treatment for a malignancy. This series includes 7 patients with breast carcinoma and AVN, an association not reported at other institutions; 1 patient with uterine carcinoma who received radiation to the region but no chemotherapy; and 5 other patients who received radiation to the hip along with chemotherapy. Radiation therapy for suspected malignancy may therefore contribute to avascular necrosis to a greater degree than previously described, further emphasizing the importance of correctly differentiating between metastases and AVN.

Steroids were included in all chemotherapeutic regimens (average 13.1 gm, range 0.6 gm—60 gm) and have previously been implicated as a risk factor for the development of avascular necrosis of the femoral head. In contradistinction to other reports, in this series Hodgkin's disease and lymphoma patients are in the minority; however, all the underlying malignancies tend to metastasize to bone.

Five of the twelve patients had bilateral hip disease, and 7 of the 17 diseased hips required total hip replacement. Onset time from chemotherapy initiation to symptomatic onset averaged 38.5 months (range, under 1 month to 132 months). Five of the patients had additional conditions that must be considered significant risk factors for the development of AVN.

The etiology of avascular necrosis is reviewed in the context of risk factors present in these patients. Patients in this series are compared to patients in reports published previously. Their risk factors are also presented and reviewed.

Avascular necrosis of the femoral head is an infrequent complication of chemotherapeutic regimens currently employed in the treatment of Hodgkin's disease, non-Hodgkin's lymphoma, and breast cancer (1–8). Estimates of its incidence range from 1.3% (1) to 5% (3). In 1980 Perloff and Lesnick published case reports of 2 patients receiving chemotherapy for breast cancer who developed avascular necrosis of the femoral head (3). This report describes all patients at The Mount Sinai Medical Center who developed avascular necrosis while being treated for a neoplastic disease from 1970 to 1983. Of the 190 patients who exhibited AVN of the femoral head in that period, 12 patients were noted to have developed the condition while being treated for a malignancy. Five of these patients had another medical condition with a previously well-documented link to avascular necrosis of the femoral head (Table 1).

Of the 12 patients in this series, 7 had the primary diagnosis of breast cancer and AVN of the femoral head, a situation unreported elsewhere. These 7 constitute an incidence of 0.13% of the 5250 patients who had breast cancer at

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TABLE 1

Conditions Associated with the Development of Avascular Necrosis of the Femoral Head

Alcoholism
Antiinflammatory agents (13)
Arthritis (degenerative and rheumatoid)
Caisson disease
Cushing's disease
Fabry's disease
Gaucher's disease
Giant cell arteritis
Gout and hyperuricemia
Hemoglobinopathies
Hyperparathyroidism
Infection
Multiple injuries or burns
Pancreatitis
Polyarteritis nodosa
Pregnancy
Radiation treatment
Scleroderma
Sickle cell disease (especially S-C) and trait
Steroid treatment
Systemic lupus erythematosus
Trauma (femoral neck fractures or dislocations)

Mount Sinai from 1970 to 1983. Two patients in this series had Hodgkin's disease or malignant lymphoma, the conditions dominating previous reports. Approximately 655 patients with Hodgkin's disease and 1,300 patients with malignant lymphoma were seen at Mount Sinai from 1970 to 1983.

Table 2 presents summarized case reports for the patients in this series with respect to age, underlying malignancy, chemotherapy, time of onset from chemotherapy initiation to AVN symptoms, and additional risk factors, including steroids, radiation, and AVN-associated conditions. A review of the literature revealed 30 additional patients being treated for a malignancy who developed avascular necrosis. Case reports on these patients are similarly summarized in Table 3.

Results

Our series had a greater percentage of women (10/12 versus 12/30) and an older group (average age, 55 years versus 33 years) than previously reported series. Seven of our twelve patients had an underlying breast cancer, whereas 27 of the 30 in prior reports (Table 3) had either Hodgkin's disease or lymphoma. These malignancies were treated with either MOPP (mechlorethamine, vincristine, procarbazine, prednisone) or COPP (cyclophosphamide instead of mechlorethamine). Most of the breast cancer patients in our series were treated with CMFVP (cyclophosphamide, methotrexate, 5-fluorouracil,

TABLE 2

Summary Case Reports, 12 Patients Seen at The Mount Sinai Medical Center

Pt. no.	Sex	Age	Underlying malignancy	Chemotherapy	Prednisone (gm)	Regional radiation (rads)	Femoral head AVN diagnosis	Pain onset (mo)	Treatment	Other risks
1	F	48	Breast (III) Ca	CMFVP	1.465	—	RL x-ray	14	RL THR	7 wk steroids for ulcerative colitis
2	F	62	Breast Ca	CMFVP	1.235	—	R x-ray bone scan	9	R THR	
3	F	43	Breast (I) Ca	CMFVP	+	—	R path	58	R Jewett Nail	Right and left adrenalectomy with steroids replaced
4	F	62	Breast Ca	—	16	—	RL and both shoulders, bone scan	132	—	SLE, RhA, Asp
5	F	41	Breast Ca	—	60	12,200	RL both shoulders, rt knee bone scan	102	—	—
6	F	47	Breast (IV) Ca	CMFVP Andriomyisis	0.61	2,000	L path	15	L THR	—
7	F	61	Breast (IV) Ca	Tamoxifen CMFVP VAF VATH	1.65	2,000	RL and shoulders, x-ray bone scan	20	—	—
8	M	40	Hodgkin's IV B	MOPP	2	+	L x-ray	37	L THR	
9	F	64	Lymphoma	cytoxan bleomycin vincristine prednisone	22	2,000	RL and shoulder x-ray	37	L THR	Uric acid, 8.5 mg/dl
10	F	75	Endometrial (II) Ca	—	—	6,500	L x-ray	2	—	—
11	M	63	Prostate	prednisone DES	+	6,500	R path	36	R Austin-Moore	Alcohol, prednisone for asthma ?Lupus ?Scleroderma
12	F	57	Cervix (squamous cell)	—	—	?	R path	1	R THR	Alcohol pancreatis

RL, both femoral heads; R, right femoral head; L, left femoral head; THR, total hip replacement.

TABLE 3

Summary Case Reports, 30 Patients Cited in the Literature

Pt. no.	Sex	Age	Underlying malignancy	Chemo-therapy	Prednisone (gm)	Regional radiation (rads)	Femoral head AVN diagnosis	Pain onset (mo)	Treatment	Other risks
1	M	66	Lymphoma IIIA	MOPP	2.52	—	RL x-ray	23	Wheelchair	EtOH
2	M	45	Hodgkin's (MC) IIIB	MOPP	2.73	—	R x-ray	21	Crutches	—
3	M	40	Lymphoma IVA	CVP	26	—	L x-ray	50	Cane	—
4	M	24	Hodgkin's (MC) IIA	MOPP	2.1	—	RL x-ray	21	—	Uric acid
5	M	33	Hodgkin's (MC)	COPP	5	—	1 x-ray, bone scan, path	21	Phemister bone grafts	—
6	F	29	Hodgkin's (NS)	COPP	4.2	—	1 x-ray, bone scan, path	28	Phemister bone grafts	—
7	F	31	Hodgkin's (NS)	COPP	3.5	—	RL x-ray, bone scan, path	39	RL THR	
8	F	54	Lymphoma	COPP	5.7	—	1 x-ray, bone scan, path	26	RL THR	Osteoarthritis
9	F	22	Hodgkin's (MC) IIB	MOPP	6.3	+	L x-ray, bone scan, path	19		
10	F	26	Hodgkin's (NS) IIB	MOPP	10.28	—	L x-ray	32		
11	F	43	Hodgkin's (NS) IV	MOPP	13.2	—	L x-ray, path	12	L joint reconstruction	—
12	M	22	Hodgkin's IIIB	C, V, MOPP	+	5,000	RL, both humeral heads, x-ray, path	21	R arthroplasty	—
13	M	21	Hodgkin's NS IIIB	MOPP	+	—	RL x-ray	12	—	—
14	M	26	Hodgkin's	MOPP	+	+	RL x-ray, path	27	R THR	
15	M	23	Hodgkin's (MC) IVB	MOPP	+	+	RL, rt. humeral head, x-ray	18		
16	M	40	Hodgkin's (MC) IVB	MOPP	14.12	*(6/9)	R x-ray	48		
17	M	40	Hodgkin's (NS) IA	MOPP	13.5	*(6/9)	L x-ray	60	Analgesics	
18	M	39	Hodgkin's (NS) IVB	MOPP	2.88	*(6/9)	RL x-ray	15		
19	F	21	Hodgkin's (MC) IIIB	MOPP	6.0	1,500	RL x-ray, path	36	RL THR	
20	M	25	Hodgkin's (NS) IVA	MOPP	6.0	*(6/9)	L x-ray, path	17	L THR	
21	F	45	Hodgkin's (MC) IA	MOPP	6.9	*(6/9)	RL x-ray, path	52	R THR	
22	M	32	Hodgkin's (NS) IIIB	MOPP	7.0	*(6/9)	RL x-ray, path	72	RL THR	
23	F	38	Hodgkin's (NS) IIA	MOPP	18.75	*(6/9)	L x-ray	24		
24	M	57	Lymphoma	MOPP	6	*(6/9)	RL x-ray, path	24	RL THR	
25	F	29	Mycosis fungoides		15	*(6/9)	rt shoulder x-ray	24		
26	M	24	Hodgkin's IIIB	COP MOPP	1.4	4,000	RL x-ray, path	8	L Wagner resurfacing	
27	F	37	Hodgkin's (NS) IA	—	—	3,500	RL x-ray	1		
28	M	22	Testicular teratoma	Vincristine Bleomycin	—	—	L both femoral condyles, x-ray scan	20		
29	M	15	Burkitt's lymphoma	Cyclophosphamide	—	—	Tibial tubercle x-ray	12		
30	F		Breast ca	CMF	—	5,600	Head of humerus x-ray			

(NS), nodular sclerosing type; (MC), mixed cellular type; R, right hip; L, left hip; x-ray, path, bone scan = method of AVN diagnosis.
* (6/9): 6 of 9 patients received radiation to region.

vincristine, prednisone), although 3 of the 12 patients, including 2 breast cancer patients, were treated without the use of cytotoxic chemotherapeutic agents.

Eight patients in our series received known quantities of steroids averaging 13.12 gm/patient. This includes 5 patients who each received less than 2.1 gm total and 3 patients who each got more than 15 gm (range 0.61 gm–60 gm). Previous reports show 22 patients with AVN and a known intake averaging 8.14 gm (range 1.4 gm–26 gm).

Radiation treatment including the femoral heads was given to 6 of the 12 patients in our series, in doses ranging from 2,000 rads to 6,500 rads, and including at least 2 patients (no. 6 and no. 11) treated for suspected metastases to the femoral head which were later shown to be AVN by pathology. Of the patients in previous reports with AVN, at least 14 of 30 (Table 3) received

TABLE 4
Summary of Case Reports

Patient group	No.	Sex	Avg age	Cancer	Chemotherapy	Regional radiation	Pain onset avg (mo)	Surgical hips	THR	Other risks
Table 2	12	10/12 F	55	7/12 breast	CMFVP	6/12	38.5	9/24	7	6/12
Table 3	30	12/30 F	33	27/30 Hodgkin's or lymphoma	MOPP	14/30	27	20/60	16	3/30
Breast Ca only	7	7/7 F	52	Breast	CMFVP 5/7	2/7	50	5/14	4	4/7

THR, total hip replacement.

radiation therapy to the region of the femoral heads. In our series, hip pain was noted at an average of 38.5 months after the initiation of therapy (range, less than 1–132 months), most between 9 and 37 months of initiation. This is longer than onset of pain in previous reports, which averages 27 months (range 1–72 months).

In most cases the diagnosis of avascular necrosis of the femoral head was made radiographically although bone scans and confirming pathology reports are documented in some cases. Eventual treatment for the avascular necrosis of the femoral head and other conditions previously linked to AVN is also summarized in Tables 2 and 3. Table 4 compares the data in previously published cases with those of our series.

Discussion

The association between therapy for a malignancy and the development of avascular necrosis of the femoral head was first presented by Ihde and DeVita in 1975 (1), a report followed by many other reports of patients developing AVN while being treated for Hodgkin's disease or lymphoma (1, 2, 4–6). From our experiences and these reports, five general risk factors—underlying malignancy, steroids, radiation therapy to the region, cytotoxic chemotherapeutic agents, and predisposing conditions in the patient—seem to be related to the association between cancer therapy and avascular necrosis of the femoral head.

Underlying Malignancy. Hodgkin's disease, lymphomas, and breast cancer of any cell type or stage have been associated with AVN of the femoral head. Testicular teratoma, prostate cancer, and endometrial carcinoma have each been implicated by a single case. The absence of lung cancer and cancers of the gastrointestinal tract and the tendency for Hodgkin's disease, lymphomas, and breast cancer to metastasize to bone suggest that these conditions themselves may play a role in the development of AVN of the femoral head. Humeral factors that weaken bone have been suggested (6).

The majority (7 of 12) of our patients had varying stages of breast cancer as the underlying malignancy. One patient had Hodgkin's disease and 1 had lymphoma, the underlying malignancies most commonly associated with AVN in the literature.

Steroids. Sincce 1957 treatment with steroids has been reported as being associated with the development of avascular necrosis (9). In 1968, 154 cases of avascular necrosis in which the patient was treated with steroids for an underlying condition not normally associated with AVN were reviewed (10). The now well-recognized association between steroid therapy and avascular necrosis of the femoral head is supported by many studies, but not supported by others (11). Interestingly, no experimental data are available indicating that corticosteroids directly cause necrosis of bone. Proposed mechanisms for steroid-induced avascular necrosis of bone include fat embolism, osteoporosis with microtrauma, steroid change in blood coagulation, and vasculitis. Since no consistent relationships have been found (6, 12–14), all these proposed mechanisms have been challenged.

Supporting the premise that steroids play a role in the development of AVN of the femoral head is the fact that steroids were used in 37 of the 42 patients whose cases we are reviewing here (Tables 2, 3). An attempt has been made to eliminate the toxic effect of steroids from the treatment regimen. Wolin et al (15) and DeVita et al (16) reported comparable survival rates in patients treated chemotherapeutically with and without steroids. However, the British National Lymphoma Investigation reported a dramatic reduction in the complete remission rate, from 80% with MOPP to 44% with MOP, in stage IV disease (17). This suggests that removal of prednisone to reduce the toxic effects during treatment might adversely affect the long-term results of treatment in a large percentage of patients.

Radiation Therapy to the Hip and Pelvis. The adverse effect of radiation therapy in the development of avascular necrosis in patients with an underlying malignancy appears to have been underestimated. Although well established as a clinical entity, AVN of the femoral head has not been viewed as a common complication. In a large series of Hodgkin's disease patients treated by radiotherapy, Kaplan (18) reported that only 1 patient developed a pathologic fracture. Goodman and Sherman (19) described radionecrosis as an infrequent occurrence with irradiation, indicating that 5,000 rads is necessary to produce a fracture of the femoral neck (20, 21). Apparently a dose exceeding 3,000 rads is required before definite radiographic changes are noted (19). These studies were reported in patients who did not receive concomitant MOPP therapy as a complicating factor.

Supporting the conclusion that radiotherapy is a major risk factor in producing avascular necrosis is our finding that 48% (20/42) of the patients reviewed here (Tables 2 and 3) received radiation to the femoral head during their therapy. Of those whose radiation amounts are known, 60% (6/10) received doses exceeding the previously cited 3,000-rad threshold (19). Particularly interesting are 2 patients (Table 2, no. 10; Table 3, no. 27) who received neither chemotherapy nor steroids, but developed AVN 2 months and 1 month after completing radiation treatments of 6,500 rads and 3,500 rads, respectively. Furthermore, Obrist et al (8) reported the case of a patient who developed AVN of the humeral head who received chemotherapy with no steroids and 5,600 rads to the humeral head.

Radiation therapy is a recognized treatment for metastatic disease to the hip but increases the risk for developing avascular necrosis of the femoral head. Therefore, the importance of a correct differential diagnosis for hip pain in a patient being treated for a malignancy cannot be overemphasized. Patients with Hodkin's disease, lymphoma, or breast cancer who develop hip pain must be carefully evaluated for AVN of the femoral head to avoid the use of radiation for nonexistent metastases. It seems appropriate that radiation to the hip be removed from certain cancer treatment regimens.

Cytotoxic Chemotherapeutic Agents. Reports of 3 patients who developed AVN while being treated with chemotherapeutic agents without steroids clearly implicate these agents as a potential contributory factor in the development of avascular necrosis of the femoral head (1, 7, 8). One patient (7), who had a testicular teratoma initially treated with vinblastine and bleomycin, developed avascular necrosis of the left femoral head, left scaphoid, and both medial femoral condyles.

The agents most often given to patients who eventually develop AVN—mechlorethamine, vincristine (Oncovin), procarbazine, and prednisone (MOPP)—are given to treat Hodgkin's disease or malignant lymphoma. Cyclophosphamide sometimes replaces mechlorethamine (COPP or C-MOPP). The breast cancer chemotherapeutic regimen of cyclophosphamide, methotrexate, 5-fluorouracil, vincristine, and prednisone (CMFVP) is implicated in the development of AVN by its presence in the treatment of 5 of our 12 patients (Table 2). Whether cytotoxic chemotherapeutic agents are actually a major risk factor for the development of AVN, are acting synergistically with the other four risk factors dicussed here, or are merely present coincidentally in these patients remains to be answered. It should be remembered, however, that thousands of patients with lung cancer and other malignancies have received the same drugs with no reported AVN complications. Lung cancer is rarely treated with prednisone, but tends to metastasize to bone, emphasizing the role of steroids in AVN development and deemphasizing the role of cytotoxic chemotherapeutic agents and underlying malignancies that metastasize to bone in AVN development. At this time cytotoxic chemotherapeutic agents have not been shown to cause avascular necrosis of the femoral head.

Other Conditions Associated with AVN. Many conditions (Table 1) have been associated with the development of avascular necrosis by themselves or after treatment with high-dose steroids. When these conditions are present simultaneously with treatment of a malignancy and hip pain, the diagnosis of avascular necrosis of the femoral head must be suspected.

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Mirror-Image Intracerebral Hemorrhages In a Patient with Systemic Lupus Erythematosus

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Abstract

A 42-year-old woman with systemic lupus erythematosus had signs and symptoms of a spontaneous left intracerebral hemorrhage. One week after successful drainage by a CT-guided needle, a second mirror-image hematoma developed in the right temporal lobe and resulted in auditory agnosia. The differential diagnoses of spontaneous intracerebral hematoma and cortical deafness, the neuroradiologic studies, and the indications for neurosurgical intervention are briefly discussed.

Systemic lupus erythematosus was originally regarded as a febrile illness with primarily cutaneous manifestations. Subsequent investigations have better defined an autoimmune collagen vascular disease with widespread involvement of the skin, serous membranes, kidneys, heart, liver, spleen, blood vessels, lymphatics, and central and peripheral nervous system. Microinfarcts and microscopic areas of hemorrhage in the brain are present at autopsy in the majority of patients with systemic lupus erythematosus (1). Neurologic manifestations may include seizures, psychiatric disorders, visual disturbance, nystagmus, vertigo, choreiform movements, intention tremor, aphasia, paresis, and meningismus (2–4). Spontaneous intracerebral hematoma is most often caused by hypertension, but may be related to an aneurysm, arteriovenous malformation, neoplasm, coagulopathy, or collagen vascular disease (5). The value of computerized tomography (CT) in the diagnosis of intracranial bleeding has been well established (6).

Case Report. A 42-year-old woman was admitted after the sudden onset of cephalgia, obtunded mental status, and weakness in the right arm and leg. Family members brought the patient to the emergency room. During the week prior to admission, she complained of visual blurring and consulted an ophthalmologist, whose findings were nondiagnostic.

Significant in her medical history was the onset of diffuse joint pain at age 23. A working diagnosis of rheumatoid arthritis was made, and aspirin and prednisone therapy was begun. Six years later, her physical findings included ulnar deviation of the fingers of both hands, splinter hemorrhages in the distal phalanges, periungual erythema, and subcutaneous nodules over both elbows. Laboratory testing for the LE phenomenon was positive. At age 30, Raynaud's phenomenon was first observed. Her medication was slowly tapered over a period of two years. At age 35, acute exacerbation of polyarthritis necessitated reinstitution of prednisone therapy. Two years later, she first experienced transient blurring of her vision and developed chondritis of both pinnae. At age 38, ibuprofen therapy was started; her chest x-ray revealed a lung nodule in the right upper lobe.

On neurologic testing, there was expressive aphasia as well as right hemiparesis, hyperreflexia, and hemisensory loss. Babinski's sign was present on the right side. Funduscopic examination was unremarkable.

Laboratory findings included positive fluorescent antinuclear antibody with a titer of

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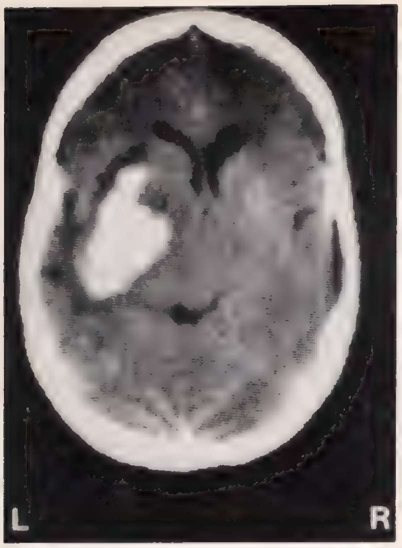

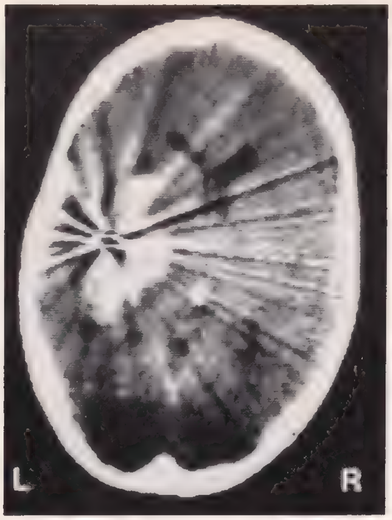

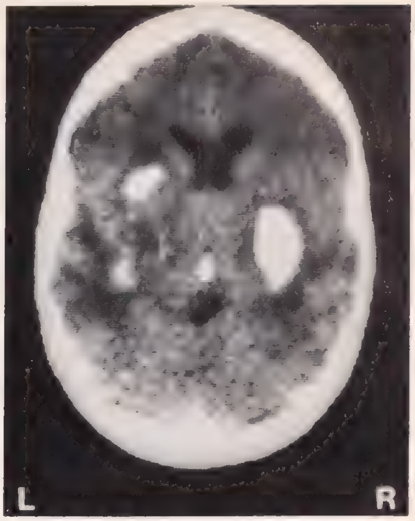

Fig. 1. Left Extensive deep left frontotemporoparietal intracerebral hematoma with definite mass effect. **Fig. 2. Middle** Obvious needle artifact in geographic center of lesion during drainage procedure. **Fig. 3. Right** Resolving left hematoma following aspiration and smaller fresh right frontotemporoparietal hemorrhage.

1/320, negative rheumatoid factor, low total serum complement (35 mg%), normal C3 serum complement (95 mg%), low anti-DNA level (<1 mg), and high Raji cell assay (2508 mg). All renal function findings, including serum creatinine, were within normal limits. Hematologic studies ruled out any coagulopathy.

An emergency CT revealed a left intracerebral hemorrhage (Fig. 1). The scalp was marked at the level of the scan revealing the greatest diameter of the lesion. The patient underwent a small temporoparietal craniectomy. Repeat scanning (Fig. 2) facilitated controlled-needle aspiration of the hematoma. About 50 cc of semisolid clot was removed; the histologic slides were unremarkable. In the immediate postoperative period, her neurologic examination was unchanged. She required steroid therapy for episodic hypotension. On the seventh hospital day, she became lethargic and unresponsive to verbal stimuli. A follow-up CT (Fig. 3) showed a mirror-image hemorrhage on the right side. Since there was no midline shift and the left intracerebral hematoma did not recur, further neurosurgical intervention was deferred. Serial CT scans documented complete resolution of both hematomas.

The patient was transferred to a rehabilitation center for six months of physiotherapy. Her mentation and speech improved, and she regained full use of her right side. As soon as she was able to cooperate, evoked brain stem potentials were tested, and auditory function was detected through the inferior colliculi. Pure tone audiometry was consistent with cortical deafness. Instruction in speech reading allowed her to become functionally independent, and she was discharged home on continuing doses of prednisone. During a four-year follow-up period, her neurologic status has been stable.

Discussion. The basic neuropathophysiologic mechanism in systemic lupus erythematosus is microangiopathy (1–4). True arteritis of major cerebral vessels has been unusual but perivascular infiltrates of inflammatory cells have often been seen. Fibrinoid degeneration in the walls of capillaries and arterioles, as well as thrombus formation, are regular features. In areas of hemorrhage, necrosis of the vessel wall may occur with extravasation of red cells. Even multiple microinfarcts do not form a pathognomonic lesion comparable to the renal wire-loop or the splenic onionskin.

Loss of hearing is practically always the result of disease of the peripheral portion of the auditory nerve. Cortical deafness is extremely rare because the auditory pathways are both crossed and uncrossed. Central deafness may occur in patients with disseminated sclerosis or tumor involving the midbrain, but only bilateral temporal lobe lesions can produce auditory agnosia.

The size of an intracerebral hematoma may be limited by clotting at the bleeding site and the tamponade effect of rising intracranial pressure. Because the white matter is split apart and not necessarily destroyed, focal deficits can resolve. Drainage of intracerebral hematomas without formal craniotomy and extensive cortical incision is possible by CT-guided needle (6). Intervention should be reserved for those cases manifesting brainstem compression due to midline shift.

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Gastric Fundic Gland Polyposis Without Familial Adenomatosis of Colon: A Report of 3 Cases

V. S. VENKATASESHAN, M.D., TE-HUNG WOO, M.D., SWAN N. THUNG, M.D., AND FREDERIC E. WIEN, M.D.

Abstract

Three cases of gastric fundic gland polyposis in elderly women are reported. This is a rare and benign hamartomatous condition mainly affecting the fundus and body of the stomach. It is usually but not always associated with familial polyposis of the colon. The gastric polyps are composed of proliferating fundic glands containing a variety of cell types with parietal cells predominating. The clinical presentation is that of nonspecific abdominal complaints. Three-fourths of the patients are women; peak incidence is in the 5th and 6th decades. It is not known whether polyp evolution or persistence depends on the hormonal status of the patient. There appears to be no relation to serum gastrin or histamine levels. Clinical and morphologic recognition of this entity can avert aggressive surgery.

Gastric polyps are relatively uncommon. A variety of benign polyps have been found in the stomach, including hyperplastic, adenomatous, and hamartomatous polyps (Peutz-Jegher's type) and familial polyposis (1). An unusual form of "hamartomatous" polyp with cystic changes, which occurs mainly in the mucosa of the fundus or body of the stomach, contains only epithelial elements and consists predominantly of parietal (oxyntic) cells. This lesion has been observed in patients with familial polyposis of the colon (2, 3). Several authors from Europe and Japan documented fundic gland polyposis as a separate clinicopathologic entity (4–8). Choi and coworkers (9) found similar lesions in 8 patients. We report on 3 patients with such polyps with microcystic changes restricted to the fundus and body of the stomach and not associated with familial adenomatosis of colon.

Case Reports

Case 1. A 72-year-old woman with a long history of asthma and emphysema was admitted to the hospital with severe wheezing and shortness of breath of two days' duration with no relief from oral theophylline. In addition, she complained of pain in the right upper quadrant and had two episodes of jaundice, the last being seven years ago. There was no significant family history. On admission the patient appeared to be dyspneic. The abdomen was slightly distended with tenderness in the right upper quadrant. Routine admission laboratory results were within normal limits, except for a positive test for occult blood in the stool. The serum gastrin and histamine levels were within normal limits.

Radiologic examination of the gastrointestinal series revealed no abnormalities of the esophagus. The stomach showed persistent round filling defects in the body, most of which had the appearance of polyps (Fig. 1). A barium enema with air contrast was normal. Ultrasound examination of the gall bladder suggested the presence of gallstones. An esophagogastroduodenoscopy showed multiple grapelike soft polypoid masses

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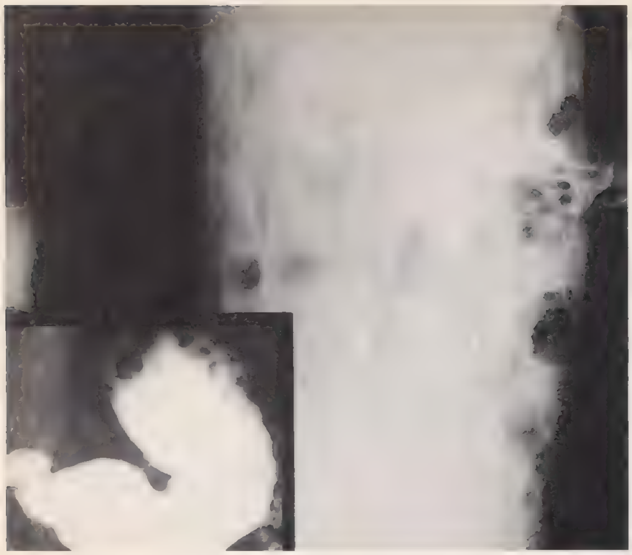

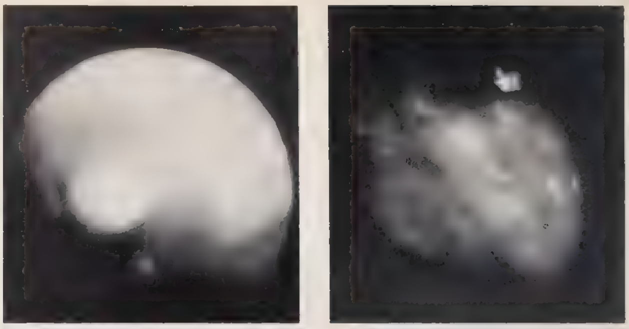

Fig. 1. Left, Case 1: X-ray of stomach with barium meal showing multiple small spherical filling defects mainly in fundus and portion of body. **Inset:** low-power view of entire stomach.
Fig. 2. Middle, Case 2: Endoscopic picture of fundus of stomach showing smooth, sessile polyps protruding into lumen. **Right, Case 3:** Endoscopic picture of body of stomach showing multiple mucosal polyps.

in the cardia and fundus; the antral mucosa was unremarkable. The polyps were biopsied. Multiple small superficial ulcers were noted in the duodenal bulb and the second part of the duodenum. The patient was given cimetidine to relieve her dyspepsia and was discharged on oral theophylline therapy for the wheezing. A week later she underwent cholecystectomy. The gallbladder showed chronic cholecystitis with cholelithiasis. One year later, the patient has occasional wheezing and dyspeptic symptoms which are relieved by bronchodilators and antacids.

Case 2. This patient, a 68-year-old woman, complained of abdominal pain and nausea. She had been taking cimetidine for a small hiatal hernia and propanolol for hypertension. Except for mild epigastric tenderness, physical examination was unremarkable. Routine laboratory tests were normal. Test for occult blood was positive in the stool. Serum gastrin and histamine levels were normal. Radiologically, upper gastrointestinal series showed no abnormalities, but extensive diverticulosis of the colon was demonstrated by a barium enema. Endoscopic examination of the upper gastrointestinal tract disclosed multiple broad-based polyps ranging from 0.4 cm to 0.8 cm in diameter (Fig. 2), mainly in the proximal portion of the stomach, some of which were biopsied. In addition, a small noninflamed hiatal hernia was seen. The pyloric channel and duodenal bulb were deformed, suggesting the presence of a chronic duodenal ulcer. On total colonoscopy there was a small solitary adenomatous polyp in the ascending colon. The patient was treated symptomatically and was treated with cimetidine and ranitidine before discharge.

Case 3. A 78-year-old woman with a long history of arteriosclerotic cardiovascular disease and hypertension was admitted because of vomiting, diarrhea, and mild dehydration. Laboratory investigation revealed low hemoglobin 9.1 gm/dl and occult blood in the stool. The stomach contents was 6 pH and tested positive for occult blood. The serum gastrin and histamine levels were within normal limits. Radiologic examination of the gastrointestinal tract showed multiple mucosal irregularities suggestive of polyps in the proximal portion of the stomach. Barium enema and ultrasound of the abdomen were reported as within normal limits. On esophagogastroscopy numerous (over 50) small, sessile, discrete polyps covered by normal mucosa (Fig. 2) were found in the fundus and body of the stomach. These were biopsied. No ulcers were noted. The pyloric channel and duodenum appeared normal. A complete colonoscopy showed no abnormalities or evidence of polyps. The patient was treated symptomatically and discharged after the vomiting and diarrhea subsided.

Pathological Findings. Grossly, the gastroscopic specimens in all 3 cases consisted of fragments of soft pink tissue with a polypoid configuration, averaging about 0.5 cm in diameter. The tissues were fixed in 10% buffered formalin and processed for routine light microscopy. Six-micron sections were stained with hematoxylin and eosin, PAS, Alcian blue (pH 2.5)-PAS, and PTAH. Immunofluorescence studies on formalin-fixed paraffin embedded sections using human autoantibodies against parietal cells and mitochondrial antigens and rabbit antibodies to lysozyme (Dako, Santa Barbara, Calif.) by the indirect immunofluorescence and avidin-biotin complex methods were performed.

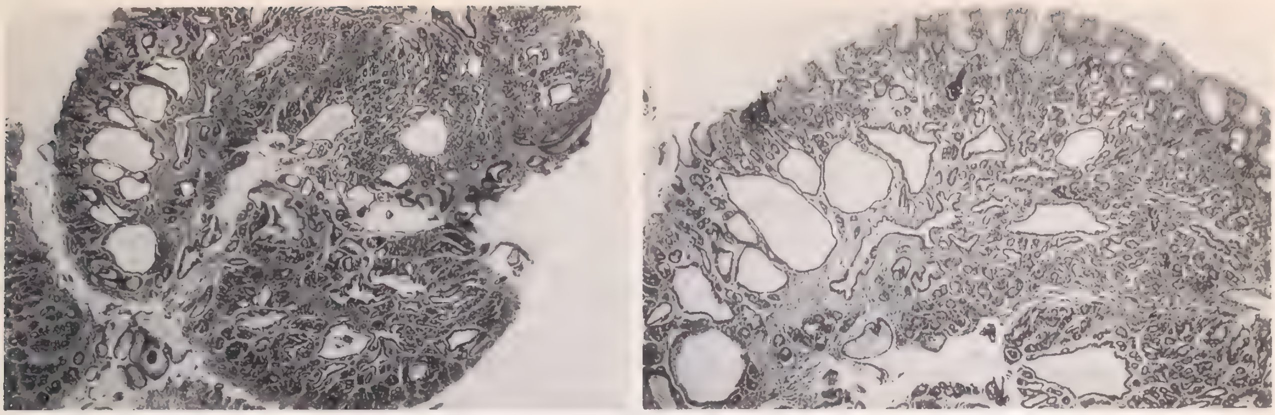

Fig. 3. **Left** Polypoid lesion of stomach showing irregularly proliferating glands with focal cystic dilation (H&E, original ×4). **Right** Higher magnification showing surface lining of normal gastric epithelium and branching glands within stroma of polyp (H&E, original ×16)

Microscopic examination of the gastric polyps in all 3 cases were similar and revealed many irregularly proliferating glands, some cystically dilated (Fig. 3). The overlying mucus-secreting columnar epithelium appeared normal. Most of the glands were arranged in clusters of varying sizes, surrounded by rather loose lamina propria and a sparse inflammatory infiltrate consisting of lymphocytes and plasma cells. Although a few were empty, several cystically dilated glands contained a small amount of granular eosinophilic, PAS-positive material in their lumina. Some glands communicated with adjacent glands and occasionally opened to the surface. All of the glands were lined predominantly by parietal cells, with granular eosinophilic cytoplasm (Fig. 4). Varying numbers of mucus secreting cells and rarely chief cells were also found scattered among the parietal cells. A few glands were lined by a single type of cell. No cytologic atypia was evident. The cells lining some dilated glands were markedly flattened. The parietal cells stained strongly with PTAH stain because of their rich mitochondrial content. The presence of mucin-producing cells was demonstrated by Alcian blue (pH 2.5) -PAS stain. In immunofluorescence studies, the parietal cells stained with antibodies to parietal cells (10) (Fig. 5), but not by antibodies to mitochondria antigens or to lysozyme. It is known that mitochondrial antigens are poorly preserved in formalin-fixed paraffin embedded tissues (11).

Discussion

Elster et al (4) recognized the special nature of the "hamartomatous" polyps, which they called fundic glandular cysts. They collected 110 cases with typical clinical and pathologic features. Sipponen and co-workers (5, 7) and Iida (8) added 52 and 23 cases found among 18,000 and 27,000 routine gastroscopic studies. Nearly 75% of the re-

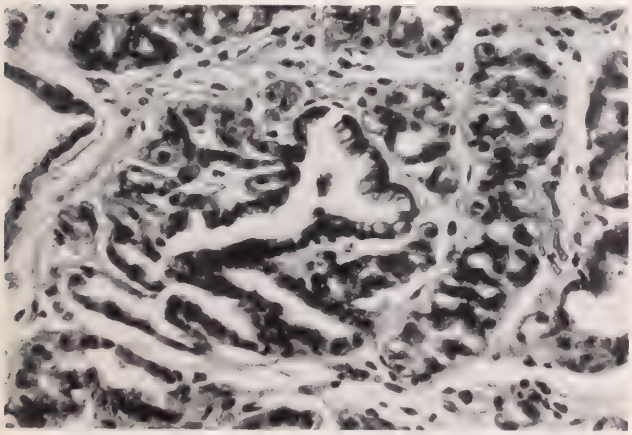

Fig. 4. **Left** Glands are lined mainly by parietal cells which stain dark and scattered clear mucus secreting cells. Mononuclear cell infiltration in stroma is minimal (H&E, original ×40).

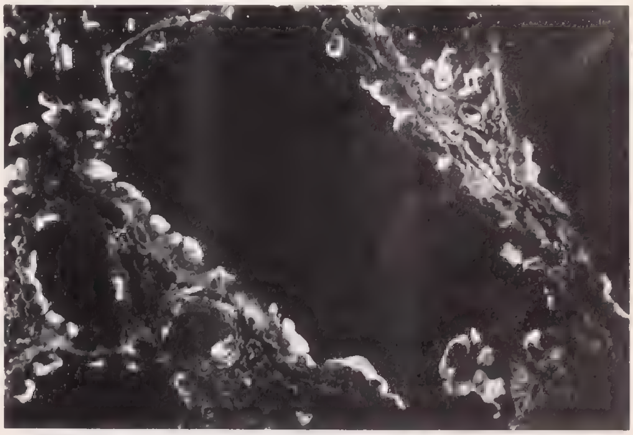

Fig. 5. **Right** Positive immunofluorescent staining of majority of cells lining cystic spaces (antiparietal cell antibodies, original ×40).

ported cases were women with nonspecific abdominal complaints, as was noted in this study. The peak incidence occurred in the 5th and 6th decade. In about 10% of patients the bleeding from the ulcers probably accounted for the presence of occult blood in the stool (7). Some patients also had cholecystitis and cholelithiasis (4).

The polyps were often multiple, arising mainly in the mucosa of the fundus and body. On radiologic and endoscopic examination they ranged from small, smooth intramucosal elevations to sessile or semisessile polypoid masses which may increase in size and number with passage of time, particularly in women. The histologic criteria supporting the hamartomatous nature of these polyps were provided by Sipponen and Suirala (5). The polyps were composed of normal epithelial elements of the mucosa of the gastric body, irregularly arranged to form proliferating, sometimes cystic, parietal glands. The surface epithelium was normal and the polyps showed no inflammation or metaplasia. These features differentiated them from gastritis cystica polyposa and the more common hyperplastic polyps which show chiefly foveolar hyperplasia (5) and are frequently accompanied by adjacent mucosal atrophy or gastritis (7, 12). Adenomatous polyps, which carry an increased risk of malignant transformation, can be easily distinguished on morphologic grounds. On rare occasion these hamartomatous polyps have been associated with Gardner's syndrome or with adenomatous or hyperplastic polyps of colon (4, 9) and small intestine (9), but generally they showed no familial tendency when not associated with familial adenomatosis of colon. Since they are recognized to be nonneoplastic and hamartomatous, there should be no tendency to malignant transformation despite recurrences and progressive enlargement of the polyps in some reported cases. Iida et al have reported spontaneous disappearance of the polyps in 3 such cases not associated with familial adenomatosis of colon (13). Gastric carcinoma was found in only 2 of 162 patients (4, 7), probably due to coincidence.

The pathogenesis of the fundic glandular "hamartomatous" polyps is not known. It was suggested that they are caused by derangement in the morphologic differentiation of parietal glands from the epithelial stem cells, which apparently does not interfere with their function (7). Microcyst formation may be secondary to focal unfolding of branching glands, and flattening of the lining cells is probably due to partial or complete retention of secretion. The predilection of polyps to postmenopausal women raises a question of the possible role of reproductive hormones. Polyp evolution does not appear to be influenced by serum gastrin or histamine, whose levels were normal in our patients.

The routine use of gastroscopy is increasing and it is important to distinguish fundic glandular "hamartomatous" polyps from other gastric lesions, both clinically and morphologically, in order to pursue proper therapy and perhaps to avoid unnecessary aggressive surgery. We suggest that a detailed family history, periodic follow-up with radiologic and endoscopic studies and barium examination of the lower gastrointestinal tract for polyps are appropriate in these patients, in order to clarify the natural history of gastric fundic gland polyposis.

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Student Corner

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Ultrasound in Diagnosis and Management of Placenta Previa at The Mount Sinai Medical Center, 1970–72 and 1981–82

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Abstract

The past decade has witnessed a marked change in the diagnosis and management of placenta previa. To examine this change and its effect on maternal and fetal outcome, I performed a retrospective study of all patients with placenta previa at The Mount Sinai Medical Center during the periods 1970–72 and 1981–82. A comparison of these two groups revealed a significant decrease in the rate of emergency cesarean sections, intrapartum and postpartum morbidity, and Apgar scores ≤ 6. The increased use of diagnostic ultrasound is believed to be responsible in part for the superior outcome of these pregnancies.

Placenta previa, in which the placenta covers all or part of the internal cervical os, usually with painless bright-red vaginal bleeding in the second half of pregnancy, occurs in approximately 1 in every 200 deliveries (1). By the 1960s the perinatal mortality rate associated with placenta previa had decreased to 11%, making it the ninth most frequent cause of perinatal death, according to the Collaborative Perinatal Project (2). The greatest threat to the infant's survival has remained preterm delivery, with resultant hyaline membrane disease. In addition, perinatal morbidity results from intrauterine growth retardation—usually asymmetric (3): 14%–16% small-for-gestational-age infants (4, 5), 7% congenital anomalies (6), 33% malpresentation (7), 1.7% cord prolapse (7), and low Apgar scores (6).

As in any disorder, the first step toward appropriate management of placenta previa is accurate diagnosis. Classically, the diagnosis was usually made by palpation of the placenta at vaginal examination under the controlled conditions of a double-setup examination (1) in an operating room or a delivery room equipped for major surgery, with available matched whole blood. A full operating team was ready, an anesthesiologist and pediatrician standing by. Since even a gentle examination could have initiated a catastrophic hemorrhage, requiring immediate delivery, it was usually undertaken only if immediate diagnosis was essential or prompt delivery was planned.

Recently, various other methods have been developed for diagnosis of placenta previa. Techniques for placental localization have evolved from soft-tissue radiography, radioisotopic placentography, arteriography, amniography, and thermography to ultrasound scan (8).

Ultrasound has several advantages over radiographic methods of placental localization. In addition to being more accurate, it is painless, convenient, noninvasive, and does not involve the use of ionizing radiation. There is, however, some concern about the safety of ultrasonic energy. It does interact with the tissue through which it passes, producing heat and cavitation. However,

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in humans, 90% of the ultrasonic intensity is dispersed by maternal soft tissue before reaching the fetus (9).

In February 1984 the National Institutes of Health concluded that, although routine use of ultrasound screening was not then indicated, diagnostic ultrasound for pregnant women improves patient management and pregnancy outcome in the presence of one of 27 clinical situations. One situation cited was vaginal bleeding of undetermined etiology in pregnancy, to determine the source of bleeding and the status of the fetus.

An extensive review of the scientific literature revealed that most of the animal studies suggestive of teratologic effects were conducted using ultrasound energy levels far in excess of those used in clinical diagnostic medicine, many under in vitro exposure conditions. Nevertheless, it was felt that these effects could not be ignored. The NIH panel encouraged further research, aimed especially at the long-term effects of exposure to ultrasound in utero.

By 1984 no confirmed reports had appeared of human fetal damage due to exposure to diagnostic levels of ultrasonic radiation. In a recent study in Denver (10), children exposed to ultrasound were compared to matched controls for adverse effects at birth and again at 7–12 years of age. Aside from a statistically insignificant excess of dyslexia and of number of hospitalizations among exposed children, consistent with the greater number of pregnancy complications in this group, no evidence was found that diagnostic ultrasound during pregnancy caused delayed physical, neurologic, or developmental harm.

This modality has initiated a new era in the diagnosis and management of placenta previa and has increased our knowledge of uteroplacental dynamics. It is now recognized, based on sonographic studies, that the relationship between the placenta and cervix changes as pregnancy progresses (11). Differential growth of the lower uterine segment may cause accelerated or decelerated growth rates in different parts of the placenta, thus producing amebalike movement along the uterine wall. The majority of patients noted to have a placenta previa during the second trimester appear to undergo placental relocation by the time of delivery. Since there is no way to distinguish a placenta that will eventually be displaced away from the cervix from one that will not, it is recommended that the ultrasound examination be repeated at two-week intervals (12).

Periodic ultrasonography helps balance the benefits of delay against the risk of another hemorrhagic episode. This enables obstetricians to navigate less precariously between the Scylla and Charybdis of maternal hemorrhage and fetal prematurity. Ultrasound has therefore assumed a prominent place in the current conservative management of placenta previa, which includes such antepartum measures as vigorous transfusion, administration of tocolytic agents to inhibit premature labor, and lecithin: sphingomyelin ratio determination to choose the most propitious time for elective delivery (7). In addition, the double-setup examination is still used because ultrasonographic diagnosis is not always definitive. One of the most dramatic changes in labor management has been the increase in the use of electronic fetal heart rate monitoring since it became available for clinical use in 1968 (13), providing an index of fetal oxygenation in order to prevent the consequences of hypoxia through appropriate intervention.

The purpose of this study is to compare the outcomes of pregnancies with placenta previa in two populations, ten years apart, in the same institution, in order to determine whether the change in the method of diagnosing placenta previa and concomitant change in management have been associated with superior maternal and fetal outcome with decreased risks.

Materials and Methods

The patient population consisted of private and clinic patients of the Department of Obstetrics and Gynecology of The Mount Sinai Medical Center in New York City. The data for this study were collected through retrospective chart review of all Mount Sinai Medical Center cases with a discharge diagnosis of total, partial, or marginal placenta previa confirmed at delivery for the years 1970–72 (Population A) and 1981–82 (Population B). These two chronologic groups were selected on the basis of expected difference in the method of diagnosis of their condition. In the early 1970s, double-setup examinations were the predominant method of diagnosis, ultrasonography being introduced on an experimental basis. Currently, ultrasound is becoming the procedure of choice in the initial evaluation of these patients, with the double-setup examination as a backup.

The limiting factors in this study were the availability of charts and the quality of the charting and coding. Of the 97 charts requested, 12 were incorrectly coded and 10 were missing.

Any omissions must be assumed to be random and introduce no bias other than lowering the apparent incidence of placenta previa.

The data were tested by chi-square analysis.

Results

Of 12,468 live births during period A, there were 29 cases of placenta previa, an incidence of 0.23%. In period B, there were 6,826 births and 28 cases of placenta previa, an incidence of 0.41%. Populations A and B were similar in number of cases of serious maternal disease. The most notable historical differences between the two populations (Table 1) were prior cesarean section rate (10% vs. 21%) and induced abortion rate (17% vs. 57%).

In the early 1970s, diagnosis was based primarily on double-setup examinations, either alone or in conjunction with ultrasound (Table 2). Other diagnostic modalities then included pelvic examination and radiography. There were two failures to diagnose cases of complete placenta previa, one by ultrasound and the other by abdominal flat plate. The 1980s group showed a statistically significant rise in utilization of ultrasound alone ($p < .001$) and a decrease in exclusive use of double setups ($p < .02$). One case of partial placenta previa was missed by ultrasound.

TABLE 1

Characteristics of Population A (1970–72) and Population B (1981–82)

	A	B
Mean maternal age (years)	30 ± 5	31 ± 5
% Ward patients	41	32
% Private patients	59	68
% Married	72	75
Parity	7	6
1–3	17	17
4–6	3	4
7+	2	1
Mean parity	2	2
Serious maternal disease*	5	5
Past ob/gyn history		
Cesarean section	3 (10%)	6 (21%)
Induced abortion	5 (17%)	16 (57%)
Spontaneous abortion	4	4
Other†	9	7
Class of placenta previa		
Total	38%	43%
Partial	52%	29%
Marginal	10%	21%
Unspecified	0%	7%

* Includes cardiovascular disease, anemia, ulcerative colitis, bronchitis, hepatitis, cirrhosis, and schizophrenia.

† Includes placenta previa, twins, ectopic gestations, postpartum hemorrhage, fetal death in utero, gestational diabetes mellitus, fibroids, dysfunctional bleeding, Asherman's syndrome, double uterus and cervix, and bicornuate uterus.

TABLE 2

Perinatal Care of Population A (1970–72) and Population B (1981–82)

	A	B
Present pregnancy problems		
1st bleed <20 wks	2	3
20–33	11	11
33–40	14	10
Mean (wks)	32	30
No bleeding	2	4
Premature rupture of membranes	8	4
Premature contractions	8	3
Diagnostic techniques		
Double setup alone	6	0 $p < 0.02$
Double setup + ultrasound	10	5
Ultrasound alone	4	22 $p < 0.001$
History alone	1	0
Diagnosed at cesarean section	2	1
Other	6	0

The cesarean section rate decreased in the two groups from 97% to 75% ($p < .05$) and the vaginal delivery rate rose from 3% to 25% ($p < .05$). More general anesthetic agents were used in Population A, and more epidurals in Population B (Table 3).

Maternal complications decreased (Table 4). There was a decrease in the rate of emergency cesarean sections ($p < .01$). Of the 10 emergency deliveries that occurred in Population A, 9 were required because of vaginal manipulation. The remaining case was one of spontaneous hemor-

TABLE 3

Characteristics of Delivery, Population A (1970–72) and Population B (1981–82)

	A	B
Method of delivery		
Vaginal	3%	25%
Cesarean section	97%	75%
Vaginal deliveries		
Partial placenta previa	1	3
Marginal placenta previa	0	3
Unspecified	0	1
Anesthesia		
Epidural	0	20
General	27	5
Other	2 spinal	1 local 2 none

TABLE 4

Maternal Outcome, Population A (1970–72) and Population B (1981–82)

	A	B	χ^2	p
Emergency cesarean section	10 (35%)	1 (4%)	8.740	<.01
Maternal morbidity				
Overall	17 (59%)	9 (32%)	4.026	<.05
Intraoperative	9 (31%)	3 (11%)	3.539	<.10
Postoperative*	14 (48%)	7 (25%)	3.317	<.10

* Infection, atelectasis, pneumonia, wound dehiscence.

rhage in a previously undiagnosed partial previa patient. The sole emergency cesarean section in Population B involved spontaneous hemorrhage in a known case of total previa which had been followed by serial sonograms.

No maternal deaths were reported in either population. The difference in number of intraoperative plus postoperative complications, 59% vs. 32%, was significant ($p < .05$). The intraoperative hemorrhages occurring in Population A necessitated blood transfusions in 7 cases and total abdominal hysterectomy in 3 patients. The 3 women in Population B with intraoperative hemorrhage required hysterectomy and transfusion.

Perinatal deaths dropped from 10% in Population A (one stillbirth, one with multiple congenital anomalies, and one with pulmonary agenesis) to 4% in Population B (one premature infant with respiratory distress syndrome). Apgar score was used as an indicator of perinatal morbidity (Table 5), at 1 min reflecting degree of antenatal asphyxia, and at 5 min predictive of subsequent morbidity and neurologic impairment (14); scores of 0–6 are considered depressed (15). Population B had an increased number of scores over 6 at 1 min ($p > .10$) and a significant increase in number of scores over 6 at 5 min ($p < .05$).

TABLE 5

Fetal Outcome, Population A (1970–72) and Population B (1981–82)

	A	B	χ^2	p
Perinatal mortality	3 (10%)	1 (4%)	1.002	>0.10
Apgar scores				
1-min				
0–6	45%	25%	2.459	>0.10
7–10	55%	75%		
5-min				
0–6	31%	7%	5.221	<0.05
7–10	69%	93%		

The babies in Population A had an average gestational length of 36 ± 5 weeks, with a mean birth weight of 2,550 ± 850 gm. In Population B, the mean gestational length was 36 ± 4 weeks and birth weight was 2,560 ± 840 gm. Data comparing the time span between initial diagnosis and delivery for the two periods were unavailable.

Discussion

There is no means of preventing placenta previa, but there are improved methods of diagnosis that improve outcome. The focus of this study was to document the increased use of diagnostic ultrasound in order to explore its effect on management and outcome. Because the study compared two populations separated by a decade, it was necessary to evaluate factors unrelated to the use of ultrasound that may have affected pregnancy outcome, such as changes in patient population, overall cesarean section rate, and coexisting high-risk conditions.

A retrospective study design was chosen as the most suitable for this investigation. For the sake of design purity, a randomized clinical trial would appear desirable at first. However, what the retrospective, observational, noninterventional study design lacks in elegance, it more than compensates for in feasibility, given the questionable ethics of withholding a form of diagnosis or treatment whose value has already been demonstrated.

The incidence of this disorder during 1970–72 and 1981–82 was low on the spectrum of reported incidences (0.3%–1.98%) (4, 6, 7, 16–24). The similarity of maternal demographic characteristics in the two populations contributed to the power of the study by keeping constant as many major parameters as possible. These women were found to have many of the risk factors reported in the literature (multiparity, prior cesarean section, induced abortion, and repeated curettage) with frequencies similar to those found by Cotton et al (7). The legalization of abortion in 1973 probably accounts for the rise in the reported induced abortion rate.

Diagnostic ultrasound was used in the early 1970s. However, it was employed only experimentally, not—as today—as the initial step in diagnosing the cause of vaginal bleeding. Enthusiasm for ultrasonography must be tempered by the realization that ultrasonographic validity depends on the expertise of the interpreter. The double-setup examination still has a place in the obstetrical diagnostic armamentarium, in the event of equivocal ultrasound readings.

While the placenta can be localized by ultrasound with close to 100% accuracy, the accuracy of ultrasonographic diagnosis of placenta previa is limited by the inherent difficulty in identification of the cervix, specifically the internal os. The rate of 4% false-negative diagnoses in Population B is consistent with the reported rates of accuracy of ultrasonographic diagnosis of placenta previa of 93%–100% (16, 25). This diagnostic dilemma arises when the fetal head in vertex presentation obscures visualization of a posterior placenta previa (12). It can often be circumvented by placing the patient in a Trendelenburg position and applying gentle upward traction on the fetal head (26) and by filling the bladder (12). Even in good hands, however, ultrasound is an imperfect tool, and false-negative diagnoses do occur. The incidence of false-positive diagnoses could not be ascertained, since confirmation of placenta previa at delivery was the criterion for inclusion in this study.

In order to determine the effect of the observed trend toward the sonogram and away from the double-setup examination over the decade of the 1970s, several maternal and fetal parameters were explored. The one that is most clearly associated with this change in diagnostic approach is the emergency cesarean section rate. There was a tenfold reduction in emergency deliveries ($p < .01$). The impact of this achievement cannot be ignored. Minimizing the necessity for vaginal manipulation, observed to precipitate 90% of the emergency situations that arose in Population A, has reduced the number of emergency deliveries along with their intrinsic hazards. The observed decrease in maternal morbidity ($p < .05$), both intraoperative and postoperative, is another important result that can be directly linked with this finding: The decline in the cesarean section rate from 97% to 75% is especially noteworthy in the face of a rise in the overall cesarean section rate from 11% in 1970–72 (27) to 21% in 1981–82 (28) at The Mount Sinai Medical Center.

Since ultrasound confers the ability to diagnose and follow pregnancies without the risk of premature intervention, one might expect to observe an increase in the length of gestation. The results of this study did not substantiate this view. Rather, the average lengths of gestation were the same in both periods. A probable explanation for this is the unreliability of the data due to a combination of poor assessment of fetal age (inaccurate dates and crude estimates by fetal size) and imprecision in the charting (for example, recording 38 weeks as "term"). In addition, the policy of expectant management introduced by Macafee (29) and Johnson (16) was adhered to in the early 1970s, delaying the performance of vaginal examination where possible. The mean gestation from both time periods, 36 weeks, is comparable to Cotton's finding of a mean gestation of 35 weeks with expectant management (7).

The birth weight statistics revealed only a very slight increment over the ten-year span, with an unchanged length of gestation. This was not an inconsistent finding, since infants of the same gestational age would not be expected to have differing weights merely because of ultrasound or electronic fetal monitoring. Factors such as prenatal care, maternal health, and nutritional status are also important.

The perinatal mortality rates compared favorably with those reported by Cotton et al (7) (12.6%) and Hibbard (30) (24.7%). Despite the fact that the small sample size precludes an unqualified statement concerning the statistical significance of these results, the data are suggestive of a trend toward improved fetal outcome. Analysis of the Apgar scores lends credibility to this apparent trend. The increased number of scores of ≥ 7 at 1 min ($p > .10$) and 5 min ($p < .05$) in Population B was consistent with this study's other findings of improved outcome for mother and baby.

Other factors must always be considered in obstetric outcome whenever time has passed. Regionalization of obstetric care and the concept of the high-risk pregnancy, introduced over the past decade, may allow for earlier identification and improved management of patients with placenta previa. In addition, electronic fetal heart rate monitoring was introduced in the years encompassed in this study; external monitors have been used routinely at The Mount Sinai Medical Center since 1975. There have been improvements in neonatal resuscitation and a shift in the preferred type of intrapartum anesthesia. The increased use of regional anesthesia, as allowed by nonemergency situations, may contribute to the lower incidence of maternal anesthesia-related respiratory complications and neonatal cardiorespiratory and neurologic depression. This parameter could not be adequately evaluated in this study because of the paucity of individuals administered regional anesthesia in Population A and general anesthesia in Population B. However, studies focusing on Apgar scores at birth have shown that, while there are more depressed newborns at 1 min with general anesthesia, by 5 min, the Apgar scores are virtually identical for both techniques (31).

Conclusions

The modern management of placenta previa includes such advances as high-risk obstetrical care, blood transfusion, electronic fetal monitoring, increased use of regional anesthesia, and neonatal resuscitation. The addition of diagnostic ultrasound to these measures, as sanctioned by the National Institutes of Health, has offered obstetricians a noninvasive alternative to the often untimely intervention of the double-setup examination. While the observed reduction in maternal and fetal compromise is testimony to the recent improvements in many aspects of obstetric and neonatal care, the contribution of ultrasound to the decrease in the emergency cesarean section rate renders it an integral part of the modern approach to the patient with placenta previa at The Mount Sinai Medical Center.

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Student Corner

Zenker's Diverticulum: Case Report and Review

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Zenker's (hypopharyngeal) diverticulum consists of a herniation of hypopharyngeal mucosa through the fibers of the inferior constrictor muscle of the pharynx. Hypopharyngeal diverticula account for 55% of all esophageal diverticula; men with the condition outnumber women approximately 3:1 (1). Zenker's diverticulum is most often seen in the elderly and is more commonly encountered today because of the increased longevity of our population. The condition was first described by Ludlow in 1769 but became associated with Zenker in 1875 after he reviewed 22 cases from the literature and added 5 of his own (2). He was the first to describe the nature of these diverticula in detail, accurately identify their anatomic location, and theorize on their etiology. The patient whose case is described below presents many of the classic signs, symptoms, and radiographic findings associated with Zenker's diverticula.

Case Report. A 60-year-old Hispanic man was admitted to the hospital because of dysphagia. His medical history was not significant. Three months prior to admission he first experienced malaise, fatigue, and weight loss of 5 lb. Three weeks prior to admission he noted the onset of dysphagia, initially to solids but progressing to include liquids. He reported retrosternal discomfort after meals, causing an almost immediate regurgitation of undigested food. The symptoms were not altered by changes in position. His dysphagia became increasingly severe 4–5 days prior to admission, virtually eliminating all oral intake. Total weight loss was 35 lb. The patient denied hematemesis, pyrosis, abdominal pain, dyspnea, or hoarseness, and had no fever, chills, or night sweats. He had not had ulcer disease, diarrhea, constipation, melena, or hematochezia. He smoked two packs of cigarettes per day for 40 years and drank one pint of Scotch each weekend for 30 years.

On admission the temperature was 97.5°F, the pulse 68, and respirations 12. The blood pressure was 130/70.

On examination the patient was cachectic. The head, lungs, heart, and skin were normal. The abdomen was soft, nontender, with normal bowel sounds. There was no peripheral edema, clubbing, or cyanosis. Examination of the genitals and rectum was normal; stool guaiac was negative. Neurologic and spine examination were both negative. A 1.5 × 1.5 cm nontender, movable lymph node was palpable in the left cervical region. The neck was otherwise normal. The buccal mucosa was dry but without lesions. The tongue was within normal limits, but poor dentition was evident. There was no coughing or gurgling in the throat associated with swallowing.

Urine was normal. Hematocrit was 36.9%; white blood cell count was 8,500; MCV was 79.7 and MCHC 32.4. Blood urea nitrogen was 15, serum glucose 91, and creatinine 1.1 mg/dl. Bilirubin was 0.5 mg/dl and protein, 6.3 g/dl (albumin 3.8 and globulin 2.5). Sodium was 141, potassium 4.4, chloride 101, and carbon dioxide 25 mEq/L. X-ray film of the chest showed a widening of the superior mediastinum. In the lateral projection, this superior mediastinal mass was indenting the trachea posteriorly. A flat and upright x-ray film of the abdomen showed a nonspecific gas pattern with no abnormal calcifications or masses identified. The bony structures were unremarkable. A barium swallow showed a large Zenker's diverticulum extending well into the mediastinum (Fig. 1). No hiatal hernia or gastroesophageal reflux was noted.

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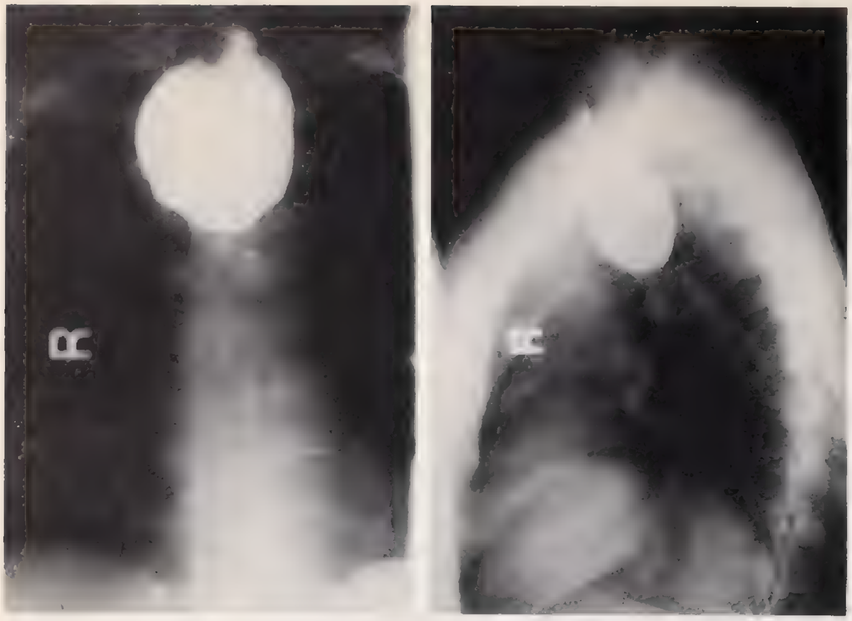

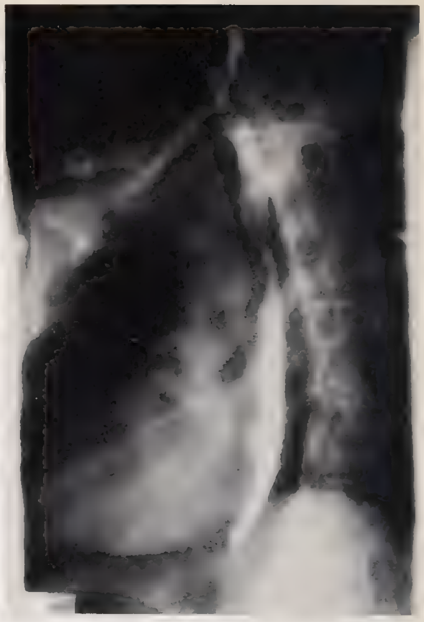

Fig. 1. Anteroposterior (**left**) and lateral (**center**) views of preoperative esophagogram showing large Zenker's diverticulum extending to superior mediastinum. **Fig. 2. Right** Esophagogram six days after diverticulectomy showing no obstruction to flow of barium, but definite narrowing at level of midcervical esophagus.

After hydration, the patient was brought to the operating room, anesthetized through endotracheal tube, and positioned with the neck extended and turned to the right. A single-stage diverticulectomy with cricopharyngeal myotomy was performed. The diverticulum measured 8.5 cm in greatest dimension.

An immediate postoperative X-ray film of the chest showed the trachea to be deviated to the right, the lungs free of infiltrates, and two radiopaque drains overlying the neck. The pathologist reported a squamous epithelial-lined diverticulum. No areas of firmness, nodularity, or ulceration were found.

The postoperative recovery was uneventful. An esophagogram performed six days after diverticulectomy showed no evidence of delay or obstruction of the barium meal (Fig. 2). No extravasation of contrast material was seen. Some divergence of the barium column occurred at the level of the midcervical esophagus and was probably due to postoperative edema. Some contrast material was seen entering the piriform sinuses and valleculae. No hiatus hernia or gastroesophageal reflux was noted. The patient was placed on an oral purée diet and discharged the following day.

Anatomy. Diverticula of the esophagus are of two types: pulsion and traction. The former include pharyngoesophageal (Zenker's) and epiphrenic diverticula. Traction diverticula occur in the midesophagus and are usually asymptomatic.

Zenker's diverticulum is a protrusion of the pharyngeal mucosa posteriorly between the oblique fibers of the thyropharyngeal portions of the inferior constrictor muscle and the transverse fibers of the cricopharyngeus muscle (3). The latter is a sling connecting the lateral borders of the cricoid cartilage and passing across the posterior wall of the esophagus. Its analog on the other end of the alimentary tract is the puborectalis sling. Cricopharyngeal tonic contraction prevents involuntary entry of air into the esophagus during respiration.

The pharyngeal constrictors are innervated by the pharyngeal plexus (4). This plexus is formed by branches of the vagus (motor), glossopharyngeal (sensory), and sympathetic nerves from the superior cervical ganglion (5). The first portion of the esophagus receives its innervation from the vagus via the recurrent laryngeal nerve. The cricopharyngeus muscle is innervated in a similar fashion to other intestinal sphincters; that is, vagal stimulation relaxes and sympathetic stimulation results in increased tone.

Etiology and Development. Zenker's diverticula are rarely encountered in patients under 30 years of age. Their fairly constant location has suggested a congenital weakness in the muscle layers of the esophagus, but the fact that they occur most commonly in men over 50 suggests that an acquired mechanism is responsible. Thus attention has been focused on the possible obstructive role of the cricopharyngeus muscle in formation of these pouches. Accordingly, a variety of disorders has been attributed to the sphincter, including spasm, premature contraction, delayed relaxation, failure of relaxation (achalasia), and reflux esophagitis.

Ellis detected a zone of elevated pressure at the pharyngoesophageal sphincter in all patients with Zenker's diverticula; sphincteric contraction occurred before completion of pharyngeal contraction. No such abnormality occurred in any of the normal patients studied (2). Furthermore, the cricopharyngeus muscle opens approximately 200 msec after peak pressure is reached in the normal hypopharynx, but in neuromuscular failure this interval is increased two- to threefold (6). Increased age with inherent changes in neuromuscular response may contribute to this dyskinesia. Thus a Zenker's diverticulum may be a high-pressure phenomenon above an area of diffuse spasm or a hyperactive sphincter.

Recently, Knuff found that resting upper esophageal sphincter (UES) pressures were significantly lower in diverticula patients than in controls (1). He concluded that symptomatic patients with Zenker's diverticula have normal pharyngoesophageal–UES coordination, exhibit complete UES relaxation on swallowing, and have low resting UES pressures. These results seriously question the previous concept of abnormalities of UES coordination as etiology of Zenker's diverticula, although the author does state that it is unclear whether his findings represent cause or effect.

Hunt found that a raised cricopharyngeal muscle tone was associated with reflux esophagitis (6). In support of this concept, Delahanty found spastic action of the cricopharyngeus muscle in conjunction with abnormal esophageal motility and gastroesophageal reflux (6). According to Delahanty, reflux esophagitis initiates disordered contractions of the esophagus and bathes the undersurface of the cricopharyngeus muscle with gastric acid, causing irritation, spasticity, and hypertrophy of this muscle.

However, Payne and Clagett believe that a hyperactive or abnormally functioning sphincter is not a common pathogenic factor in Zenker's diverticula and that the latter are related solely to a congenital weakness.

Symptoms. The symptomatology of Zenker's diverticula is quite variable. Many cases are entirely free of symptoms and require no treatment. Yet a majority of patients complain of dysphagia, regurgitation of undigested food, fullness in the throat, or loss of weight. The symptomatology varies with the stage of the disease; initially the sac is small and develops slowly, but once it is large enough, symptoms progressively worsen. As the sac enlarges, it stimulates further enlargement by torsion on and kinking of the esophageal lumen, causing food to enter the sac and not the distal esophagus. Once this occurs, the diverticulum will protrude anteriorly and to the left.

Less than half the patients experience aspiration, which is usually manifested by coughing, choking, or wheezing (7). Such symptoms are more commonly experienced at night, causing the patient to awaken with respiratory distress. Aspiration pneumonitis or, less frequently, lung abscess occurred in less than 10% of patients reviewed by Welsh and Payne. Other pulmonary complications such as bronchitis and bronchiectasis are common in long-standing diverticula (8).

Other complications include change of voice, fetid breath secondary to decomposition of food retained in the diverticulum, diverticulitis, ulceration, and even perforation. Shirazi et al describe a case of extensive ulceration in Zenker's diverticulum in a patient with gastroesophageal reflux (8). They concluded that this exceedingly rare complication probably represented peptic ulceration of the diverticular mucosa secondary to reflux of gastric acid.

Perforation may lead to esophagotracheal fistula. Senders and Babin state that such a fistula represents a malignant process in 80% of cases reported; about 80% of these patients died within three months, usually of pulmonary complications (9).

Carcinoma in a Zenker's diverticulum has been reported in only 23 instances throughout the world, with an incidence of less than 2% (10). Among published case reports, the average duration of symptoms related to the diverticulum is 17 years; therefore, carcinoma appears to occur in diverticula present for a long time. The changes most frequently noted prior to the discovery of the carcinoma were the development of hematemesis and hoarseness. Cigarette or alcohol abuse did not correlate with malignancy.

Diagnosis. The differential diagnosis of Zenker's diverticula includes stricture after caustic ingestion, Plummer-Vinson syndrome, cricopharyngeal achalasia, carcinoma of the cervical esophagus, and neurogenic dysphagia associated with such disorders as multiple sclerosis, syringomyelia, amyotrophic lateral sclerosis, myasthenia gravis, and collagen vascular disorders (6). The diagnosis is established by roentgenographic confirmation of the characteristic diverticulum on the lateral barium esophagogram. Associated findings on lateral X-rays of the neck might consist of widening of the retrotracheal soft tissue space, a retrotracheal air–fluid level, or both. When a barium-filled esophagus is seen solely from an anteroposterior view, an upper esophageal web cannot always be excluded, and therefore lateral and/or oblique views are necessary.

Ellis states that esophagoscopy is not necessary and, in fact, may be contraindicated because of the danger of accidental perforation. However, Donald and Huffman believe that the procedure is essential in all cases of Zenker's diverticulum in order to rule out carcinoma and to assess the pouch itself more accurately (10).

An irregularly shaped mass within the barium-filled diverticulum is suggestive of carcinoma but may simply be a filling defect. A Zenker's diverticulum containing an ulcer may give the radiographic impression of a malignancy, and therefore esophagoscopy is needed to differentiate the two.

Diagnosis of an esophagotracheal fistula can at times be difficult. A contrast roentgenogram usually demonstrates the fistula. The use of a catheter for the introduction of contrast material facilitates this observation because the catheter allows the contrast material to reach the diverticulum while diminishing the chances of overflow aspiration (11). Endoscopy is also necessary but not always sufficient to establish the benign or malignant nature of a fistula. Stanford et al suggest that bronchoscopy may be more productive since it avoids the mucosal folds that may hide the fistula (11). The introduction of methylene blue into the esophagus during bronchoscopy is a further aid. Finally, Biggi et al prefer to use sonography in the workup of neck masses. They state that although sonography cannot be considered the method of choice in the study of Zenker's diverticula, it should be the first imaging method used in evaluation (12).

Treatment and Surgical Complications. The only nonsurgical treatment of Zenker's diverticula is palliative continued esophageal dilatation. Many forms of surgical treatment were used in the past; however, these procedures have been replaced by one-stage diverticulectomy with or without myotomy, or cricopharyngeal myotomy alone. Rarely, endoscopic resection may be performed.

Single-stage diverticulectomy involves a verticle incision, either anterior or posterior to the sternocleidomastoid muscle. Although the former is used more frequently, the latter eliminates the need for traction on the carotid sheath and thus avoids occlusion of the carotid artery (an important consideration in the elderly patient). In either case the neck incision should be placed high enough to expose the neck rather than the fundus of the diverticulum (4). Gauze packing may be placed into the diverticulum to help localize the sac in the neck, to facilitate dissection of the muscle fibers from the mucosa of the diverticulum, and to prevent the nasogastric tube and esophageal dilator from perforating the diverticulum when they are subsequently passed into the esophageal lumen.

Once the neck of the diverticulum is free, the packing is removed and the diverticulum resected by placing either a clamp or a 30-mm stapling device transversely across its neck. Vered et al suggest that the muscular coat of the hypopharynx be approximated over the stapled stump and sutured (13). The esophageal dilator prevents excessive resection of the esophageal mucosa and prevents a stricture at the resection site. The nasogastric tube is generally removed on the fifth postoperative day and oral feedings are begun (6). The Penrose drain is removed the following day provided no leakage of esophageal secretions has occurred. Clagett and Payne, who have the largest experience with this procedure, reported a mortality rate of 0.8% in 1960 after 478 cases, but figures as high as 10% have been reported by other investigators (2).

Surgical exposure of the cricopharyngeus muscle and diverticular sac for myotomy is the same as described for diverticulectomy. After the sac is freed to its neck, transverse fibers of the cricopharyngeus muscle are easily identified and incised beginning at the inferior margin of the neck of the diverticulum. The incision is carried down to the mucosa and extended caudally on the esophagus for a total length averaging 5 cm; the cricopharyngeus itself is never more than 1.5 cm in diameter (14). The esophageal and cricopharyngeus muscles are then dissected from the underlying mucosa for about half the circumference of the mucosal tube. The cervical incision is closed in the usual way without drainage, and the patient is allowed free oral feedings, being discharged from the hospital in one or two days. This procedure is often used in combination with diverticulectomy.

Postoperative complications of one-stage diverticulectomy include infection, temporary external fistula, esophagopleural fistula, distal esophageal narrowing, recurrent laryngeal nerve injury, hemothorax, and persistent diverticulum (15). Postoperative esophagograms often show recurrent defects without functional abnormality. At least 6–12 months should be allowed to elapse before reoperation on patients who develop postoperative fistula or persistent diverticula (15). Reoperations after formal surgery can be performed endoscopically, avoiding the hazards of adhesions from previous surgery.

Although rare, infection, recurrent laryngeal nerve damage, and hemothorax are the only reported complications of cricopharyngeus myotomy. This may be due to the fact that myotomy is often combined with diverticulectomy, therefore making it difficult to attribute postoperative complications to myotomy alone.

Discussion. Review of the literature demonstrates that esophageal pressure studies do not positively establish the etiology of Zenker's diverticula. In fact, as more investigators attempt to describe their development and pathophysiology, more conflicting information is provided and additional questions are raised. Perhaps the reason multiple etiologies have been proposed for Zenker's diverticula is because multiple factors are responsible for their development. As we await the definitive study on Zenker's diverticula, the debate surrounding this issue will persist and intensify.

Less controversial is the management of patients proven to have Zenker's diverticulum. Most authors advocate the use of one-stage diverticulectomy with myotomy for large diverticula (greater than 4 cm) and myotomy alone for small and medium-sized diverticula (up to 4 cm) (14). However, Zuckerbraun and Bahna are of the opinion that myotomy alone is the only treatment for Zenker's diverticula unless there is reason to suspect ulceration or malignancy in the pouch (5).

Several advantages are gained by limiting surgery to myotomy; a shorter operating time, particularly valuable for elderly and medically compromised patients; ability to resume oral feedings immediately upon recovery from anesthesia; elimination of the need for a nasogastric tube; elimination of the risk of suture line leakage and stricture formation secondary to tight closure; elimination of the need for prophylactic antibiotics or wound drainage; and reduced hospital stay (5). Another advantage is the possibility of performing the surgery under local anesthesia. Myotomy also produces dramatic relief of dysphagia, although radiologic evidence of a smaller, contracted diverticulum persists. Occasionally a patient will have dysphagia if one or both vagus nerves are transected; such patients have improved after myotomy. Disorders of muscular function (i.e., muscular dystrophy) that cause incoordination of the cricopharyngeus muscle are also successfully treated with myotomy, whereas dysfunction that is neurologic in origin (i.e., poliomyelitis or cerebral infarct) cannot be cured with myotomy (14). Although the list of advantages is impressive, myotomy used alone for the treatment of Zenker's diverticulum remains controversial.

In a patient who is immunocompromised, a benign, self-limiting process may appear malignant. Spontaneous fistula formation and vocal cord paralysis may develop. Under such circumstances, malignancy must be vigorously searched for. If the source of the fistulization is benign, surgical treatment yields better results than nonsurgical therapy. When malignancy is a proven complication, simple excision is not the treatment of choice. Instead, wide surgical excision and en bloc radical neck dissection, followed by a full course of radiotherapy and subsequent surgical reconstruction, are required (10). Because the management of diverticula containing carcinoma is drastically different from that of a sac that is free of malignancy, preoperative esophagoscopy has been recommended by Fisher and Bond in all cases of Zenker's diverticula.

Welsh and Payne demonstrated the following conditions in approximately one-third of patients with Zenker's diverticula: esophageal hiatal hernia (73%), other esophageal diverticula (22%), esophageal achalasia (3%), diffuse spasm of the esophagus (1%), and primary carcinoma of the diverticulum (1%) (16). Holinger and Jensik found that 8% of the patients with Zenker's diverticula had other esophageal pathology in a distribution similar to that found by Welsh and Payne, with the addition of esophageal varices (10%) (17). These associated findings have not been confirmed by other investigators, nor have they been implicated in the development of Zenker's diverticula. Nonetheless, it is tempting to suggest that a congenitally weakened or maldeveloped esophagus may be more susceptible to multiple pathology than a normal esophagus, and therefore, the role of genetics in the etiology of Zenker's diverticula may be substantial.

Finally, a "new" complication has arisen in the management of patients with Zenker's diverticula; oral medications, as well as food and mucus, can accumulate in a large diverticulum leading to loss of drug bioavailability (18). Considering the insidious nature of this condition, the fact that it occurs most commonly in elderly patients, and the fact that it is this same group that consumes the majority of medications sold in this country, the issue of drug bioavailability may have far-reaching and disastrous consequences for the many patients with Zenker's diverticula.

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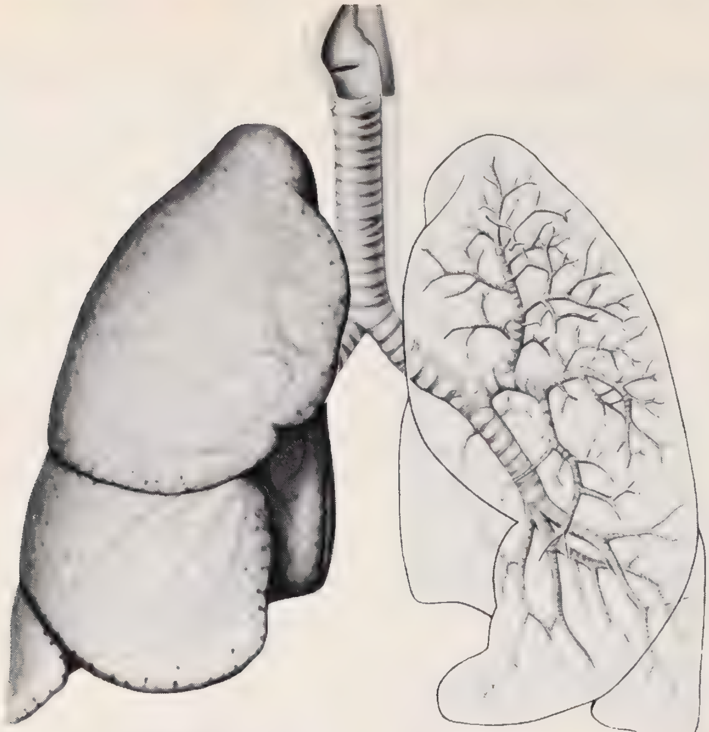

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